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By: *Sumit Butti*

Submitted herewith for filing under 37 CFR 1.53(b) is the
[X] patent application of
[] continuation patent application of
[] divisional patent application of
[] continuation-in-part patent application of

Inventor(s)/Applicant Identifier: Lawrence R. MCGEE, Jonathan B. HOUZE and Steven M. RUBENSTEIN

For: COMPOUNDS FOR THE MODULATION OF PPAR γ ACTIVITY

[X] This application claims priority from each of the following Application Nos./filing dates:

60/141,672 filed June 30, 1999

the disclosure(s) of which is (are) incorporated by reference.

[X] Please amend this application by adding the following before the first sentence: "This application claims the benefit of U.S. Provisional Application No. 60/141,672, filed June 30, 1999, the disclosure of which is incorporated by reference."

Enclosed are:

[X] 200 page(s) of specification

[X] 18 page(s) of claims

[X] 1 page of Abstract

[] sheet(s) of [] formal [] informal drawing(s).

[] An assignment of the invention to _____

[X] A [] signed [X] unsigned Declaration & Power of Attorney

[] A [] signed [] unsigned Declaration.

[] A Power of Attorney.

[] A verified statement to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27 [] is enclosed [] was filed in the prior application and small entity status is still proper and desired.

[] A certified copy of a _____ application.

[] Information Disclosure Statement under 37 CFR 1.97.

[] A petition to extend time to respond in the parent application.

[] Notification of change of [] power of attorney [] correspondence address filed in prior application.

In view of the Unsigned Declaration as filed with this application and pursuant to 37 CFR §1.53(f),
Applicant requests deferral of the filing fee until submission of the Missing Parts of Application.

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PATENT APPLICATION
COMPOUNDS FOR THE MODULATION
OF PPAR γ ACTIVITY

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COMPOUNDS FOR THE MODULATION OF PPAR γ ACTIVITY

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is related to USSN 60/073,042, filed January 29, 1998,
5 and USSN 09/234,327, filed January 20, 1999, and claims the benefit of USSN
60/141,672, filed June 30, 1999. This application is also related to PCT application
_____, filed June 28, 2000 (Attorney Docket 018781-002710PC). The disclosures
of each of the above being incorporated herein by reference in their entirety.

10 **STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT**

The invention described herein was not made with the aid of any federally
sponsored grants.

15 **FIELD OF THE INVENTION**

The present invention relates to compounds that modulate the PPAR γ
receptor and are useful in the diagnosis and treatment of type II diabetes (and
complications thereof), hypercholesterolemia (and related disorders associated with
abnormally high or low plasma lipoprotein or triglyceride levels) and inflammatory
20 disorders.

BACKGROUND OF THE INVENTION

The peroxisome proliferator-activated receptors (PPARs) are transducer
proteins belonging to the steroid/thyroid/retinoid receptor superfamily. The PPARs were
25 originally identified as orphan receptors, without known ligands, but were named for their
ability to mediate the pleiotropic effects of fatty acid peroxisome proliferators. These
receptors function as ligand-regulated transcription factors that control the expression of
target genes by binding to their responsive DNA sequence as heterodimers with RXR.
The target genes encode enzymes involved in lipid metabolism and differentiation of
30 adipocytes. Accordingly, the discovery of transcription factors involved in controlling
lipid metabolism has provided insight into regulation of energy homeostasis in
vertebrates, and further provided targets for the development of therapeutic agents for
disorders such as obesity, diabetes and dyslipidemia.

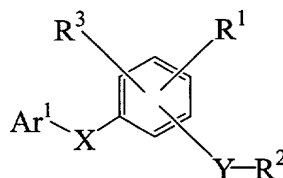
PPAR γ is one member of the nuclear receptor superfamily of ligand-activated transcription factors and has been shown to be expressed in an adipose tissue-specific manner. Its expression is induced early during the course of differentiation of several preadipocyte cell lines. Additional research has now demonstrated that PPAR γ plays a pivotal role in the adipogenic signaling cascade. PPAR γ also regulates the ob/leptin gene which is involved in regulating energy homeostasis, and adipocyte differentiation which has been shown to be a critical step to be targeted for anti-obesity and diabetic conditions.

In an effort to understand the role of PPAR γ in adipocyte differentiation, several investigators have focused on the identification of PPAR γ activators. One class of compounds, the thiazolidinediones, which were known to have adipogenic effects on preadipocyte and mesenchymal stem cells *in vitro*, and antidiabetic effects in animal models of non-insulin-dependent diabetes mellitus (NIDDM) were also demonstrated to be PPAR γ -selective ligands. More recently, compounds that selectively activate murine PPAR γ were shown to possess *in vivo* antidiabetic activity in mice.

Despite the advances made with the thiazolidinedione class of antidiabetes agents, unacceptable side effects have limited their clinical use. Accordingly, there remains a need for potent, selective activators of PPAR γ which will be useful for the treatment of NIDDM and other disorders related to lipid metabolism and energy homeostasis. Still further, compounds that block PPAR γ activity would be useful for interfering with the maturation of preadipocytes into adipocytes and thus would be useful for the treatment of obesity and related disorders associated with undesirable adipocyte maturation. Surprisingly, the present invention provides compounds that are useful as activators as well as antagonists of PPAR γ activity and compositions containing them, along with methods for their use.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides methods of modulating conditions which are mediated by PPAR γ . The methods typically involve contacting the host with a PPAR γ -modulating amount of a compound having the formula:



in which the symbol Ar^1 represents a substituted or unsubstituted aryl group; the letter X represents a divalent linkage selected from substituted or unsubstituted $(\text{C}_1\text{-C}_6)$ alkylene, substituted or unsubstituted $(\text{C}_1\text{-C}_6)$ alkylenoxy, substituted or unsubstituted $(\text{C}_1\text{-C}_6)$ alkylenamino, substituted or unsubstituted $(\text{C}_1\text{-C}_6)$ alkylene- $\text{S}(\text{O})_k$, -O-, -C(O)-, -

5 $\text{N}(\text{R}^{11})$ -, $\text{-N}(\text{R}^{11})\text{C}(\text{O})$ -, $\text{-S}(\text{O})_k$ - and a single bond, in which R^{11} is a member selected from hydrogen, $(\text{C}_1\text{-C}_8)$ alkyl, $(\text{C}_2\text{-C}_8)$ heteroalkyl and aryl $(\text{C}_1\text{-C}_4)$ alkyl and the subscript k is an integer of from 0 to 2. The letter Y, in the above formula represents a divalent linkage selected from substituted or unsubstituted $(\text{C}_1\text{-C}_6)$ alkylene, -O-, -C(O)-, - $\text{N}(\text{R}^{12})$ - $\text{S}(\text{O})_m$ -, -
10 $\text{N}(\text{R}^{12})$ - $\text{S}(\text{O})_m$ - $\text{N}(\text{R}^{13})$ -, $\text{-N}(\text{R}^{12})\text{C}(\text{O})$ -, $\text{-S}(\text{O})_n$ -, a single bond, and combinations thereof, in which R^{12} and R^{13} are members independently selected from hydrogen, substituted or unsubstituted $(\text{C}_1\text{-C}_8)$ alkyl, substituted or unsubstituted $(\text{C}_2\text{-C}_8)$ heteroalkyl and substituted or unsubstituted aryl $(\text{C}_1\text{-C}_4)$ alkyl; and the subscripts m and n are independently integers of from 0 to 2.

15 The symbol R^1 represents a member selected from hydrogen, halogen, cyano, nitro, $(\text{C}_1\text{-C}_8)$ alkyl, $(\text{C}_1\text{-C}_8)$ alkoxy, $\text{-CO}_2\text{R}^{14}$, $\text{-C}(\text{O})\text{NR}^{15}\text{R}^{16}$, $\text{-C}(\text{O})\text{R}^{14}$, $\text{-S}(\text{O})_p\text{-R}^{14}$, $\text{-S}(\text{O})_q\text{-NR}^{15}\text{R}^{16}$, $\text{-O-C}(\text{O})\text{-OR}^{17}$, $\text{-O-C}(\text{O})\text{-R}^{17}$, $\text{-O-C}(\text{O})\text{-NR}^{15}\text{R}^{16}$, $\text{-N}(\text{R}^{14})\text{-C}(\text{O})\text{-NR}^{15}\text{R}^{16}$, $\text{-N}(\text{R}^{14})\text{-C}(\text{O})\text{-R}^{17}$ and $\text{-N}(\text{R}^{14})\text{-C}(\text{O})\text{-OR}^{17}$, in which R^{14} is a member selected from hydrogen, $(\text{C}_1\text{-C}_8)$ alkyl, $(\text{C}_2\text{-C}_8)$ heteroalkyl, aryl and aryl $(\text{C}_1\text{-C}_4)$ alkyl; R^{15} and R^{16} are
20 members independently selected from hydrogen, $(\text{C}_1\text{-C}_8)$ alkyl, $(\text{C}_2\text{-C}_8)$ heteroalkyl, aryl, and aryl $(\text{C}_1\text{-C}_4)$ alkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; and R^{17} is a member selected from hydrogen, $(\text{C}_1\text{-C}_8)$ alkyl, $(\text{C}_2\text{-C}_8)$ heteroalkyl, aryl and aryl $(\text{C}_1\text{-C}_4)$ alkyl. In each of the descriptions of, for example, alkyl, alkoxy and heteroalkyl, the groups can be substituted or unsubstituted.

25 The symbol R^2 represents a substituted or unsubstituted aryl group. Preferably, R^2 represents a phenyl, naphthyl, pyridazinyl or pyridyl group. More preferably, R^2 is a phenyl, naphthyl, pyridazinyl or pyridyl group substituted with from 0-3 substituents selected from halogen, -OCF_3 , -OH , $\text{-O}(\text{C}_1\text{-C}_8)$ alkyl, -CN , -CF_3 , $\text{-C}(\text{O})\text{-(C}_1\text{-C}_8)$ alkyl, $\text{-(C}_1\text{-C}_8)$ alkyl and -NH_2 .

30 The symbol R^3 represents a halogen, cyano, nitro or a substituted or unsubstituted $(\text{C}_1\text{-C}_8)$ alkoxy group.

In another aspect, the present invention provides compounds of the formula above, as well as pharmaceutical compositions containing the compounds described above.

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DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions:

The following abbreviations are used herein: PPAR γ : peroxisome proliferator-activated receptor γ ; NIDDM: non-insulin-dependent diabetes mellitus; Et₃N: triethylamine; MeGH: methanol; and DMSO: dimethylsulfoxide.

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The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C₁-C₁₀ means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)ethyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below as "heteroalkyl," "cycloalkyl" and "alkylene." The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂-. Typically, an alkyl group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

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The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and

wherein the nitrogen and sulfur atoms are optionally oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, and -CH=CH-N(CH₃)-CH₃. Up to two heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. Also included in the term "heteroalkyl" are those radicals described in more detail below as "heteroalkylene" and "heterocycloalkyl." The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by -CH₂-CH₂-S-CH₂CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini. Still further, for alkylene and heteroalkylene linking groups, as well as all other linking group provided in the present invention, no orientation of the linking group is implied.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "fluoroalkyl," are meant to include monofluoroalkyl and polyfluoroalkyl.

The term "aryl," employed alone or in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) means, unless otherwise stated, an aromatic substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The rings may each contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the

nitrogen atom(s) are optionally quaternized. The aryl groups that contain heteroatoms may be referred to as "heteroaryl" and can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 2-benzothiazolyl, 5-benzothiazolyl, 2-benzoxazolyl, 5-benzoxazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinoliny, 5-isoquinoliny, 2-quinoxaliny, 5-quinoxaliny, 3-quinoliny, and 6-quinoliny. Substituents for each of the above noted aryl ring systems are selected from the group of acceptable substituents described below. The term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) or a heteroalkyl group (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

Each of the above terms (e.g., "alkyl," "heteroalkyl" and "aryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'C(O)NR''R''', -NR''C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -CN and -NO₂ in a number ranging from zero to (2N+1), where N is the total number of carbon atoms in such radical. R', R'' and R''' each independently refer to hydrogen, unsubstituted(C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C₁-C₄)alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like). Preferably, the alkyl groups (and related alkoxy, heteroalkyl, etc.) are unsubstituted or have 1 to 3 substituents selected

from halogen, -OR', =O, -NR'R'', -SR', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -NR''C(O)R', -S(O)₂R', -S(O)₂NR'R'', -CN and -NO₂. More preferably, the alkyl and related groups have 0, 1 or 2 substituents selected from halogen, -OR', =O, -NR'R'', -SR', -CO₂R', -CONR'R'', -NR''C(O)R', -CN and -NO₂.

5 Similarly, substituents for the aryl groups are varied and are selected from halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NR'-C(O)NR''R'', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to the
10 total number of open valences on the aromatic ring system; and where R', R'' and R''' are independently selected from hydrogen, (C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl, (unsubstituted aryl)-(C₁-C₄)alkyl, and (unsubstituted aryl)oxy-(C₁-C₄)alkyl. Preferably, the aryl groups are unsubstituted or have from 1 to 3 substituents selected from halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -
15 NR''C(O)R', -S(O)₂R', -S(O)₂NR'R'', perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl. Still more preferably, the aryl groups have 0, 1 or 2 substituents selected from halogen, -OR', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -NR''C(O)R', -S(O)₂R', -S(O)₂NR'R'', perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl.

Two of the substituents on adjacent atoms of the aryl ring may optionally
20 be replaced with a substituent of the formula wherein T and U are independently -NH-, -O-, -CH₂- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 3.
25 One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -(CH₂)_s-X-(CH₂)_t-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituent R' in -NR'- and -S(O)₂NR'- is selected from hydrogen or
30 unsubstituted (C₁-C₆)alkyl.

As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases,

depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of

5 pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically

10 acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, oxalic, maleic, malonic, benzoic,

15 succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present

20 invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical

25 properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the

30 compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

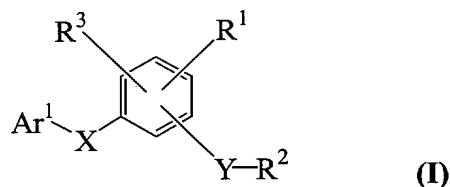
General:

A new class of compounds that interact with PPAR γ has now been discovered. Depending on the biological environment (*e.g.*, cell type, pathological condition of the host, *etc.*), these compounds can activate or block the actions of PPAR γ . By activating the PPAR γ receptor, the compounds will find use as therapeutic agents capable of modulating conditions mediated by the PPAR γ receptor. As noted above, example of such conditions is NIDDM. Additionally, the compounds are useful for the prevention and treatment of complications of diabetes (*e.g.*, neuropathy, retinopathy, glomerulosclerosis, and cardiovascular disorders), and treating hyperlipidemia. Still further, the compounds are useful for the modulation of inflammatory conditions which most recently have been found to be controlled by PPAR γ (see, Ricote, *et al.*, *Nature*, **391**:79-82 (1998) and Jiang, *et al.*, *Nature*, **391**:82-86 (1998). Examples of inflammatory conditions include rheumatoid arthritis and atherosclerosis.

Compounds that act via antagonism of PPAR γ are useful for treating obesity, hypertension, hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia, and metabolic disorders.

Embodiments of the Invention:

In one aspect, the present invention provides compounds which are represented by the formula:



In formula (I), the symbol Ar^1 represents a substituted or unsubstituted aryl group. Preferably, Ar^1 is a monocyclic or fused bicyclic aryl group having from zero to four heteroatoms as ring members. More preferably, Ar^1 is a monocyclic or fused bicyclic aryl group comprising two fused six-membered rings, two fused five-membered rings, or a six-member ring having a fused five-membered ring. heteroaryl group containing from 1 to 3 nitrogen atoms in the ring or rings. Particularly preferred embodiments are those in which Ar^1 is phenyl, naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, isoquinolinyl, benzothiazolyl, benzoxazolyl, and benzimidazolyl, with the proviso that when Ar^1 is substituted or unsubstituted 2-benzothiazolyl, then X is $-\text{S}(\text{O})_k-$ wherein the subscript k is 0, 1 or 2. As noted above, Ar^1 can be both unsubstituted and substituted. In preferred embodiments, Ar^1 is substituted with from 0 to 3 substituents selected from halogen, $-\text{OCF}_3$, $-\text{OH}$, $-\text{O}-(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{CF}_3$, $(\text{C}_1-\text{C}_6)\text{alkyl}$, or $-\text{NO}_2$. In one group of preferred embodiments, Ar^1 is a monocyclic heteroaryl group containing 1 to 2 nitrogen atoms in the ring and being monosubstituted by halogen, $-\text{OCF}_3$ or $-\text{CF}_3$. In another group of preferred embodiments, Ar^1 is a phenyl or naphthyl group having from 1 to 3 substituents selected from halogen, cyano, nitro, $(\text{C}_1-\text{C}_8)\text{alkyl}$ or $(\text{C}_1-\text{C}_8)\text{alkoxy}$.

The letter X represents a divalent linkage selected from substituted or unsubstituted $(\text{C}_1-\text{C}_6)\text{alkylene}$, substituted or unsubstituted $(\text{C}_1-\text{C}_6)\text{alkylenoxy}$, substituted or unsubstituted $(\text{C}_1-\text{C}_6)\text{alkylenamino}$, substituted or unsubstituted $(\text{C}_1-\text{C}_6)\text{alkylene-S}(\text{O})_k$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{11})-$, $-\text{N}(\text{R}^{11})\text{C}(\text{O})-$, $-\text{S}(\text{O})_k-$ and a single bond, in which R^{11} is a member selected from hydrogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$ and $\text{aryl}(\text{C}_1-\text{C}_4)\text{alkyl}$ and the subscript k is an integer of from 0 to 2. In preferred embodiments, X represents $-\text{O}-$, $-\text{C}(\text{O})-$, substituted or unsubstituted $(\text{C}_1-\text{C}_6)\text{alkylene}$, $-\text{N}(\text{R}^{11})-$, or $-\text{S}(\text{O})_k-$. Most preferably, X represents $-\text{O}-$, $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_2\text{CH}_3)-$, $-\text{CH}(\text{isopropyl})-$, -

CH(CN)-, -C(O)-, -N(R¹¹)-, or -S(O)_k-. Still further preferred are those embodiments in which X represents -O-, -CH₂-, -CH(CH₃)-, -C(O)-, -N(R¹¹)-, or -S(O)_k-, wherein R¹¹ is hydrogen, methyl, ethyl, propyl and isopropyl.

The letter Y, in the above formula represents a divalent linkage selected from substituted or unsubstituted (C₁-C₆)alkylene, -O-, -C(O)-, -N(R¹²)-S(O)_m-, -N(R¹²)-S(O)_m-N(R¹³)-, -N(R¹²)C(O)-, -S(O)_n-, a single bond, and combinations thereof, in which R¹² and R¹³ are members independently selected from hydrogen, substituted or unsubstituted (C₁-C₈)alkyl, substituted or unsubstituted (C₂-C₈)heteroalkyl and substituted or unsubstituted aryl(C₁-C₄)alkyl; and the subscripts m and n are independently integers of from 0 to 2. In preferred embodiments, Y represents -N(R¹²)-S(O)₂- or -N(R¹²)-C(O)-. More preferably, Y represents -N(R¹²)-S(O)₂- in which R¹² is hydrogen or substituted or unsubstituted (C₁-C₈)alkyl. Most preferably, Y represents -NH-S(O)₂-. Additionally, the linkages provided herein (represented by X and Y) can be in either orientation. More particularly, for example, the nitrogen atom of -N(R¹²)-S(O)₂- can be attached to either the central benzene ring or to the R² group.

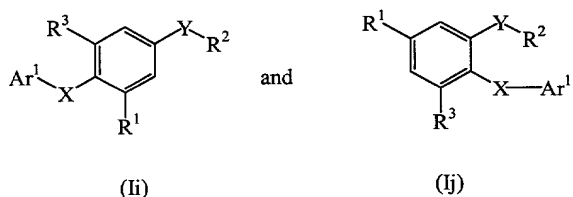
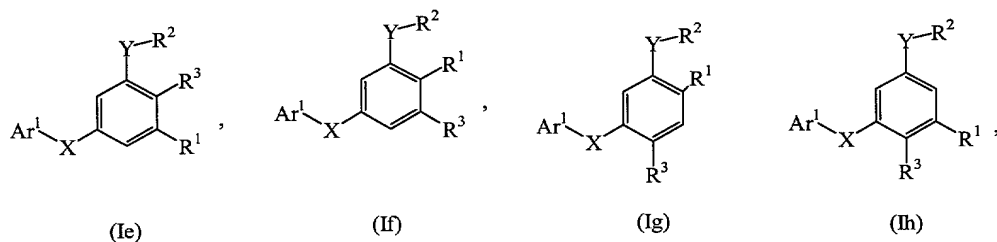
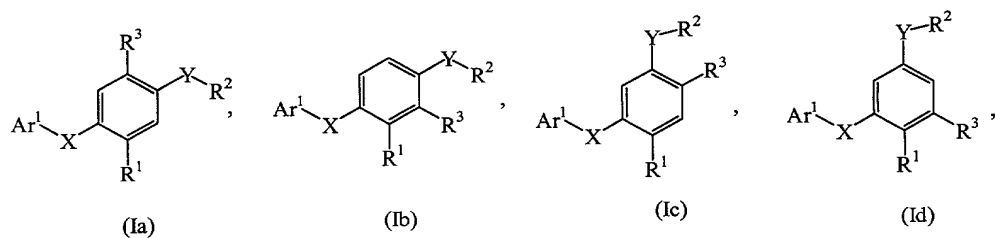
The symbol R¹ represents a member selected from hydrogen, halogen, cyano, nitro, (C₁-C₈)alkyl, (C₁-C₈)alkoxy, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -C(O)R¹⁴, -S(O)_p-R¹⁴, -S(O)_q-NR¹⁵R¹⁶, -O-C(O)-OR¹⁷, -O-C(O)-R¹⁷, -O-C(O)-NR¹⁵R¹⁶, -N(R¹⁴)-C(O)-NR¹⁵R¹⁶, -N(R¹⁴)-C(O)-R¹⁷ and -N(R¹⁴)-C(O)-OR¹⁷, in which R¹⁴ is a member selected from hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, aryl and aryl(C₁-C₄)alkyl; R¹⁵ and R¹⁶ are members independently selected from hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, aryl, and aryl(C₁-C₄)alkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; and R¹⁷ is a member selected from hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, aryl and aryl(C₁-C₄)alkyl. In each of the descriptions of, for example, alkyl, alkoxy and heteroalkyl, the groups can be substituted or unsubstituted. Preferably, when substituted the substituents are halogen (e.g., -CF₃, -OCF₃). In preferred embodiments, R¹ represents hydrogen, halogen, cyano, (C₁-C₈)alkyl, (C₁-C₈)alkoxy, -CO₂R¹⁴ and -C(O)NR¹⁵R¹⁶. More preferably, R¹ represents hydrogen, halogen, cyano, (C₁-C₈)alkyl, (C₁-C₈)alkoxy, -CO₂R¹⁴ and -C(O)NR¹⁵R¹⁶ in which R¹⁴ is (C₁-C₈)alkyl, and R¹⁵ and R¹⁶ are independently hydrogen or (C₁-C₈)alkyl, or taken together with the nitrogen to which each is attached form a 5- or 6-membered ring. Other preferred R¹ groups are discussed below with reference to groupings of compounds wherein Ar¹ is phenyl, pyridyl, naphthyl, quinoliny, isoquinoliny, benzoxazolyl, benzothiazolyl and benzimidazolyl.

The symbol R^2 represents a substituted or unsubstituted aryl group. Preferably, R^2 represents a phenyl, naphthyl, pyridazinyl or pyridyl group. More preferably, R^2 is a phenyl, naphthyl, pyridazinyl or pyridyl group substituted with from 0-3 substituents selected from halogen, $-OCF_3$, $-OH$, $-O(C_1-C_8)alkyl$, $-CN$, $-CF_3$, $-C(O)-(C_1-C_8)alkyl$, $-(C_1-C_8)alkyl$ and $-NH_2$. While certain preferred substituents have been provided (e.g., $-OCF_3$ and $-CF_3$), the terms alkyl and alkoxy are also meant to include substituted versions thereof, preferably halosubstituted versions including those specifically noted.

The symbol R^3 represents a halogen, cyano, nitro or a substituted or unsubstituted $(C_1-C_8)alkoxy$ group, preferably a halogen, cyano or $(C_1-C_4)alkoxy$ group. Most preferably, halogen, methoxy or trifluoromethoxy.

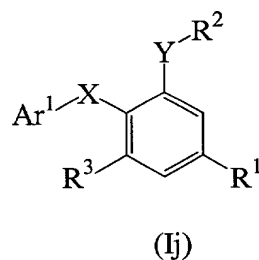
A number of preferred embodiments are provided herein. For example, in one preferred embodiment, X is a divalent linkage selected from $-CH_2-$, $-CH(CH_3)-$, $-O-$, $-C(O)-$, $-N(R^{11})-$ and $-S-$; and Y is $-N(R^{12})-S(O)_2-$, wherein R^{12} is a member selected from hydrogen and $(C_1-C_8)alkyl$. In another preferred embodiment, X is a divalent linkage selected from $-CH_2-$, $-CH(CH_3)-$, $-O-$, $-C(O)-$, $-N(R^{11})-$ and $-S-$; Y is $-N(R^{12})-S(O)_2-$, wherein R^{12} is a member selected from hydrogen and $(C_1-C_8)alkyl$; and R^2 is a substituted or unsubstituted aryl selected from phenyl, pyridyl, naphthyl and pyridazinyl. In yet another preferred embodiment, X is a divalent linkage selected from $-CH_2-$, $-CH(CH_3)-$, $-O-$, $-C(O)-$, $-N(R^{11})-$ and $-S-$; Y is $-N(R^{12})-S(O)_2-$, wherein R^{12} is a member selected from hydrogen and $(C_1-C_8)alkyl$; R^2 is a substituted or unsubstituted aryl selected from phenyl, pyridyl, naphthyl and pyridazinyl; and Ar^1 is a substituted or unsubstituted aryl selected from pyridyl, phenyl, naphthyl, quinoliny, isoquinoliny, benzoxazolyl, benzothiazolyl, and benzimidazolyl.

One of skill in the art will understand that a number of structural isomers are represented by formula I. In one group of embodiments, the isomers are those in which the groups on the phenyl ring occupy positions that are not contiguous. In other embodiments, the compounds are those having the structural orientations represented by the formulae:

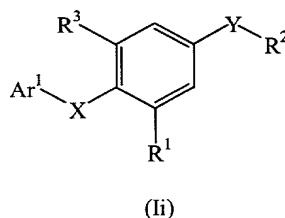


Still further preferred are those compounds having the structural orientation represented by formula Ia or Ib. Still other preferred compounds, are those of formula Ia or Ib in which the positions of R¹ and R³ are switched (or reversed).

5 Yet other preferred compounds are those in which Ar¹-X- and -Y-R² occupy positions ortho to one another (exemplified by Ij).



Still another group of preferred compounds are represented by the formula:



Ar¹ is substituted or unsubstituted phenyl

In one group of particularly preferred embodiments, Ar¹ is a substituted or unsubstituted phenyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar¹ is substituted or unsubstituted phenyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from -CH₂-, -CH(CH₃)-, -O-, -C(O)-, -N(R¹¹)- and -S-, wherein R¹¹ is a member selected from hydrogen and (C₁-C₈)alkyl; Y is a divalent linkage selected from -N(R¹²)-S(O)₂-, wherein R¹² is a member selected from hydrogen and (C₁-C₈)alkyl; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴, -S(O)_q-NR¹⁵R¹⁶, -O-C(O)-R¹⁷, and -N(R¹⁴)-C(O)-R¹⁷, wherein R¹⁴ is a member selected from hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, aryl and aryl(C₁-C₄)alkyl; R¹⁵ and R¹⁶ are members independently selected from hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R¹⁷ is a member selected from hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R² is a substituted or unsubstituted phenyl; and R³ is a halogen or (C₁-C₈)alkoxy.

In further preferred embodiments, X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar¹ is a phenyl group having from 1 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₆)alkyl, -CF₃, (C₁-C₈)alkyl and -NO₂; R¹ is a member selected from halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and (C₁-C₈)alkoxy; R² is a phenyl group having from 0 to 3 substituents selected from

halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂, more preferably 1 to 3 substituents selected from halogen, -OCF₃ and -CF₃; and R³ is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred
5 embodiments are those in which R¹ and R³ are each independently a halogen, and R² is a phenyl group having from 1 to 3 substituents selected from halogen, -OCF₃, and -CF₃.

Ar¹ is substituted or unsubstituted pyridyl

In one group of particularly preferred embodiments, Ar¹ is a substituted or unsubstituted pyridyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are
10 those embodiments in which X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen,
15 methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar¹ is substituted or unsubstituted pyridyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from -CH₂-, -CH(CH₃)-, -O-, -C(O)-, -N(R¹¹)- and -S-, wherein R¹¹ is a member selected from hydrogen and (C₁-C₈)alkyl; Y is a divalent linkage selected from -N(R¹²)-S(O)₂-, wherein R¹² is a member
20 selected from hydrogen and (C₁-C₈)alkyl; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴, -S(O)_q-NR¹⁵R¹⁶, -O-C(O)-R¹⁷, and -N(R¹⁴)-C(O)-R¹⁷, wherein R¹⁴ is a member selected from hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, aryl
25 and aryl(C₁-C₄)alkyl; R¹⁵ and R¹⁶ are members independently selected from hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R¹⁷ is a member selected from hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R² is a substituted or unsubstituted phenyl; and R³ is a halogen or (C₁-C₈)alkoxy.

30 In further preferred embodiments, X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-

C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar¹ is a pyridyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₆)alkyl, -CF₃, (C₁-C₈)alkyl and -NO₂; R¹ is a member selected from halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and (C₁-C₈)alkoxy; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂, more preferably 1 to 3 substituents selected from halogen, -OCF₃ and -CF₃; and R³ is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R¹ and R³ are each independently a halogen, and R² is a phenyl group having from 1 to 3 substituents selected from halogen, -OCF₃, and -CF₃. Most preferably, Ar¹ is a 3-pyridyl group having preferred substituents as indicated above.

In still other particularly preferred embodiments, the compounds are represented by formula I, in which Ar¹ is a pyridyl ring having a single substituent selected from halogen, -OCF₃ and -CF₃; X is a divalent linkage selected from the group of -O-, -C(O)-, -CH₂- and combinations thereof; Y is a divalent linkage selected from the group of -NH-S(O)₂- and -NH-C(O)-; R¹ is selected from hydrogen, halogen, cyano, (C₁-C₈)alkyl, (C₁-C₈)alkoxy and -C(O)NR¹⁵R¹⁶ in which R¹⁵ and R¹⁶ are selected from hydrogen, (C₁-C₈)alkyl, aryl and aryl(C₁-C₄)alkyl; R² is a phenyl or pyridyl ring, optionally substituted by 0-3 groups selected from halogen, (C₁-C₈)alkyl, -O-(C₁-C₈)alkyl and -CN; and R³ is halogen, cyano or (C₁-C₄)alkoxy.

Ar¹ is substituted or unsubstituted naphthyl

In one group of particularly preferred embodiments, Ar¹ is a substituted or unsubstituted naphthyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar¹ is substituted or unsubstituted naphthyl, are those that are represented by either of formulae Ii or Ij. In this

group of embodiments, X is a divalent linkage selected from $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{11})-$ and $-\text{S}-$, wherein R^{11} is a member selected from hydrogen and $(\text{C}_1-\text{C}_8)\text{alkyl}$; Y is a divalent linkage selected from $-\text{N}(\text{R}^{12})-\text{S}(\text{O})_2-$, wherein R^{12} is a member selected from hydrogen and $(\text{C}_1-\text{C}_8)\text{alkyl}$; R^1 is a member selected from hydrogen, halogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$, $(\text{C}_1-\text{C}_8)\text{alkoxy}$, $-\text{C}(\text{O})\text{R}^{14}$, $-\text{CO}_2\text{R}^{14}$, $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{16}$, $-\text{S}(\text{O})_p-\text{R}^{14}$, $-\text{S}(\text{O})_q-\text{NR}^{15}\text{R}^{16}$, $-\text{O}-\text{C}(\text{O})-\text{R}^{17}$, and $-\text{N}(\text{R}^{14})-\text{C}(\text{O})-\text{R}^{17}$, wherein R^{14} is a member selected from hydrogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$, aryl and aryl $(\text{C}_1-\text{C}_4)\text{alkyl}$; R^{15} and R^{16} are members independently selected from hydrogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R^{17} is a member selected from hydrogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$; the subscript p is an integer of from 0 to 2; the subscript q is 2; R^2 is a substituted or unsubstituted phenyl; and R^3 is a halogen or $(\text{C}_1-\text{C}_8)\text{alkoxy}$.

In further preferred embodiments, X is $-\text{O}-$, $-\text{NH}-$ or $-\text{S}-$; Y is $-\text{NH}-\text{SO}_2-$; R^1 is a member selected from hydrogen, halogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$, $(\text{C}_1-\text{C}_8)\text{alkoxy}$, $-\text{C}(\text{O})\text{R}^{14}$, $-\text{CO}_2\text{R}^{14}$, $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{16}$, $-\text{S}(\text{O})_p-\text{R}^{14}$ and $-\text{S}(\text{O})_q-\text{NR}^{15}\text{R}^{16}$; R^2 is a phenyl group having from 0 to 3 substituents selected from halogen, $-\text{OCF}_3$, $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_8)\text{alkyl}$, $-\text{C}(\text{O})-(\text{C}_1-\text{C}_8)\text{alkyl}$, $-\text{CN}$, $-\text{CF}_3$, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $-\text{NH}_2$; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar^1 is a naphthyl group having from 0 to 3 substituents selected from halogen, $-\text{OCF}_3$, $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{CF}_3$, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $-\text{NO}_2$; R^1 is a member selected from halogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$ and $(\text{C}_1-\text{C}_8)\text{alkoxy}$; R^2 is a phenyl group having from 0 to 3 substituents selected from halogen, $-\text{OCF}_3$, $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_8)\text{alkyl}$, $-\text{C}(\text{O})-(\text{C}_1-\text{C}_8)\text{alkyl}$, $-\text{CN}$, $-\text{CF}_3$, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $-\text{NH}_2$, more preferably 1 to 3 substituents selected from halogen, $-\text{OCF}_3$ and $-\text{CF}_3$; and R^3 is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substituents selected from halogen, $-\text{OCF}_3$, and $-\text{CF}_3$.

Ar^1 is substituted or unsubstituted benzothiazolyl

In another group of particularly preferred embodiments, Ar^1 is a substituted or unsubstituted benzothiazolyl group, with the proviso that when Ar^1 is substituted or unsubstituted 2-benzothiazolyl, then X is $-\text{S}(\text{O})_k-$. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is $-\text{O}-$, $-\text{NH}-$ or $-\text{S}-$; Y is

phenyl group having from 1 to 3 substituents selected from halogen, -OCF₃, and -CF₃. In particularly preferred embodiments, the benzothiazolyl group is a 2-benzothiazolyl group.

Ar¹ is substituted or unsubstituted benzoxazolyl

In another group of particularly preferred embodiments, Ar¹ is a substituted or unsubstituted benzoxazolyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar¹ is substituted or unsubstituted benzoxazolyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from -CH₂-, -CH(CH₃)-, -O-, -C(O)-, -N(R¹¹)- and -S-, wherein R¹¹ is a member selected from hydrogen and (C₁-C₈)alkyl; Y is a divalent linkage selected from -N(R¹²)-S(O)₂-, wherein R¹² is a member selected from hydrogen and (C₁-C₈)alkyl; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴, -S(O)_q-NR¹⁵R¹⁶, -O-C(O)-R¹⁷, and -N(R¹⁴)-C(O)-R¹⁷, wherein R¹⁴ is a member selected from hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, aryl and aryl(C₁-C₄)alkyl; R¹⁵ and R¹⁶ are members independently selected from hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R¹⁷ is a member selected from hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R² is a substituted or unsubstituted phenyl; and R³ is a halogen or (C₁-C₈)alkoxy.

In further preferred embodiments, X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar¹ is a benzoxazolyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₆)alkyl, -CF₃, (C₁-

C₈)alkyl and -NO₂; R¹ is selected from halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and (C₁-C₈)alkoxy; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂, more preferably 1 to 3 substituents selected from halogen, -OCF₃ and -CF₃; and R³ is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R¹ and R³ are each independently a halogen, and R² is a phenyl group having from 1 to 3 substituents selected from halogen, -OCF₃, and -CF₃. In particularly preferred embodiments, the benzoxazolyl group is a 2-benzoxazolyl group.

Ar¹ is substituted or unsubstituted benzimidazolyl

In another group of particularly preferred embodiments, Ar¹ is a substituted or unsubstituted benzimidazolyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar¹ is substituted or unsubstituted benzimidazolyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from -CH₂-, -CH(CH₃)-, -O-, -C(O)-, -N(R¹¹)- and -S-, wherein R¹¹ is a member selected from hydrogen and (C₁-C₈)alkyl; Y is a divalent linkage selected from -N(R¹²)-S(O)₂-, wherein R¹² is a member selected from hydrogen and (C₁-C₈)alkyl; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴, -S(O)_q-NR¹⁵R¹⁶, -O-C(O)-R¹⁷, and -N(R¹⁴)-C(O)-R¹⁷, wherein R¹⁴ is a member selected from hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, aryl and aryl(C₁-C₄)alkyl; R¹⁵ and R¹⁶ are members independently selected from hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R¹⁷ is a member selected from hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R² is a substituted or unsubstituted phenyl; and R³ is a halogen or (C₁-C₈)alkoxy.

In further preferred embodiments, X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-

C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen, methoxy and trifluoromethoxy.

- 5 In still further preferred embodiments, Ar¹ is a benzimidazolyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₆)alkyl, -CF₃, (C₁-C₈)alkyl and -NO₂; R¹ is selected from halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and (C₁-C₈)alkoxy; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂, more preferably 1 to 3 substituents selected from halogen, -OCF₃ and -CF₃; and R³ is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred
10 embodiments are those in which R¹ and R³ are each independently a halogen, and R² is a phenyl group having from 1 to 3 substituents selected from halogen, -OCF₃, and -CF₃. In particularly preferred embodiments, the benzimidazolyl group is a 2-benzimidazolyl
15 group.

Ar¹ is substituted or unsubstituted quinolinyl or isoquinolinyl

- In another group of particularly preferred embodiments, Ar¹ is a substituted or unsubstituted isoquinolinyl group. Further preferred are those
embodiments in which the compound is represented by any of formulae Ia through Ij.
20 Still further preferred are those embodiments in which X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen, methoxy and trifluoromethoxy.
25

- Other particularly preferred embodiments wherein Ar¹ is substituted or unsubstituted isoquinolinyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from -CH₂-, -CH(CH₃)-, -O-, -C(O)-, -N(R¹¹)- and -S-, wherein R¹¹ is a member selected from hydrogen and (C₁-C₈)alkyl; Y is a divalent linkage selected from -N(R¹²)-S(O)₂-, wherein R¹² is a member
30 selected from hydrogen and (C₁-C₈)alkyl; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴, -S(O)_q-NR¹⁵R¹⁶, -O-C(O)-R¹⁷, and -N(R¹⁴)-C(O)-R¹⁷, wherein R¹⁴ is a member selected from hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, aryl

and aryl(C₁-C₄)alkyl; R¹⁵ and R¹⁶ are members independently selected from hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R¹⁷ is a member selected from hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R² is a substituted or unsubstituted phenyl; and R³ is a halogen or (C₁-C₈)alkoxy.

In further preferred embodiments, X is -O-, -NH- or -S-; Y is -NH-SO₂-; R¹ is a member selected from hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar¹ is an isoquinolinyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₆)alkyl, -CF₃, (C₁-C₈)alkyl and -NO₂; R¹ is selected from halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and (C₁-C₈)alkoxy; R² is a phenyl group having from 0 to 3 substituents selected from halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂, more preferably 1 to 3 substituents selected from halogen, -OCF₃ and -CF₃; and R³ is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R¹ and R³ are each independently a halogen, and R² is a phenyl group having from 1 to 3 substituents selected from halogen, -OCF₃, and -CF₃. In particularly preferred embodiments, the isoquinolinyl group is selected from 3-isoquinolinyl and 4-isoquinolinyl groups.

In another aspect, the present invention provides pharmaceutical compositions comprising at least one of the above compounds in admixture with a pharmaceutically acceptable excipient.

In yet another aspect, the present invention provides methods for modulating conditions mediated by PPAR_γ in a host. More particularly, the conditions are selected from non-insulin-dependent diabetes mellitus, obesity, conditions associated with abnormal plasma levels of lipoproteins or triglycerides, and inflammatory conditions such as, for example, rheumatoid arthritis and atherosclerosis.

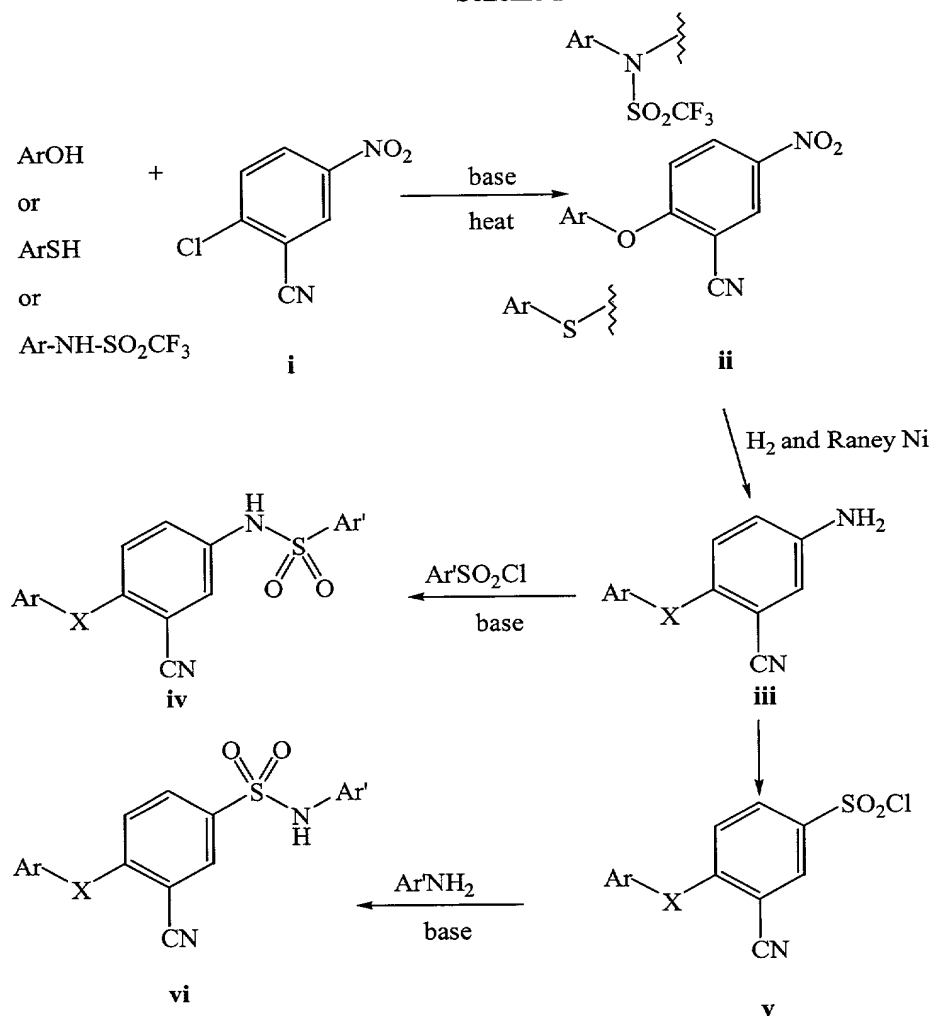
Preparation of the Compounds

The compounds of the present invention can be prepared using standard synthetic methods. For exemplary purposes, Scheme 1 illustrates methods for the

preparation of compounds of structural formula (Ia). One of skill in the art will understand that similar methods can be used for the synthesis of compounds in the other structural classes.

As shown in Scheme 1, compounds of the present invention can be
5 prepared beginning with commercially available 2-chloro-5-nitrobenzonitrile (i). Treatment of J with a phenol, thiophenol, or optionally protected aniline in the presence of base and heat provides the adduct (ii). Reduction of the nitro group in ii with, for example, H₂ in the presence of Raney nickel catalyst provides an aniline derivative (iii).
10 Sulfonylation of iii with an appropriate arylsulfonyl halide (Ar¹ SO₂C₁) in the presence of base (typically a tertiary amine) provides a target compound (iv). Compound iii can also be converted to a related compound of formula (vi) in which the orientation of the sulfonamide linkage is reversed. Thus, conversion of the aniline iii to the benzenesulfonyl chloride v can be accomplished using methods described in Hoffman, Organic Syntheses Collective Volume VII, p. 508-511. Subsequent treatment of v with
15 an appropriate aniline provides the target compound vi.

Scheme 1



Other compounds of the present invention can be prepared beginning with, for example, 3,4-difluoronitrobenzene, 3-chloro-4-fluoronitrobenzene, 2-chloro-5-nitroanisole, 3-bromo-4-fluoronitrobenzene and the like.

5

Analysis of the Compounds

The compounds of the present invention can be evaluated for modulation of the PPAR γ receptor using assays such as those described in Jiang, *et al.*, *Nature* **391**:82-86 (1998), Ricote, *et al.*, *Nature* **391**:79-82 (1998) and Lehmann, *et al.*, *J. Biol. Chem.* **270**(12): 12953-12956 (1995). Alternatively, the compounds can be evaluated for their ability to displace radiolabeled BRL 49653 from a PPAR γ -GST fusion protein as follows:

10

Materials:

PPAR γ -GST fusion protein (prepared according to standard procedures),
[³H]-BRL 49653 having 50 Ci/mmol specific activity, Polyfiltronics Unifilter 350
filtration plate and glutathione-Sepharose® beads (from Pharmacia: washed twice with
5 10x binding buffer in which BSA and DTI can be left out).

Method:

Binding buffer (10 mM Tris-HCl, pH 8.0, 50 mM KCl, 10 mM DTT,
0.02% BSA and 0.01% NP-40) is added in 80 microliter amounts to the wells of the
filtration plate. The test compound is then added in 10 microliters of DMSO. The
10 PPAR γ -GST fusion protein and radiolabeled BRL compound are premixed in binding
buffer containing 10 mM DTT and added in 10 microliter amounts to the wells of the
plate to provide final concentrations of 1 μ g/well of PPAR γ -GST fusion protein and 10
nM [³H]-BRL 49653 compound. The plate is incubated for 15 minutes. Glutathione-
agarose bead is added in 50 μ L of binding buffer, and the plate is vigorously shaken for
15 one hour. The plate is washed four times with 200 μ L/well of binding buffer (without
BSA and DTT). The bottom of the plate is sealed and 200 μ L/well of scintillation
cocktail is added. The top of the plate is then sealed and the radioactivity is determined.

Formulation and Administration of the Compounds (Compositions)

20 The compounds of the present invention can be prepared and administered
in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the
present invention can be administered by injection, that is, intravenously, intramuscularly,
intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the
compounds described herein can be administered by inhalation, for example, intranasally.
25 Additionally, the compounds of the present invention can be administered transdermally.
Accordingly, the present invention also provides pharmaceutical compositions
comprising a pharmaceutically acceptable carrier or excipient and either a compound of
formula (I) or a pharmaceutically acceptable salt of a compound of formula (I).

For preparing pharmaceutical compositions from the compounds of the
30 present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid
form preparations include powders, tablets, pills, capsules, cachets, suppositories, and
dispersible granules. A solid carrier can be one or more substances which may also act as

diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1000 mg, preferably 1.0 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if
10 desired, also contain other compatible therapeutic agents.

In therapeutic use for the treatment of obesity, NIDDM, or inflammatory conditions, the compounds utilized in the pharmaceutical method of the invention are administered at the initial dosage of about 0.001 mg/kg to about 100 mg/kg daily. A daily dose range of about 0.1 mg/kg to about 10 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following examples are offered by way of illustration and are not intended to limit the scope of the invention.

EXAMPLES

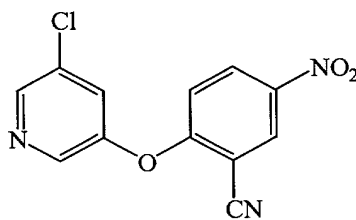
Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ¹H-NMR spectra were recorded on a Varian Gemini 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Electron Ionization (EI) mass spectra were recorded on a Hewlett Packard 5989A mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses). In tables, a single m/e value is reported for the M+H (or as noted M-H) ion containing the most common atomic

isotopes. Isotope patterns correspond to the expected formula in all cases. Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard 1100 MSD electrospray mass spectrometer using the HP1 100 HPLC for sample delivery. Normally the analyte was dissolved in methanol at 0.1mg/mL and 1 microliter was infused with the delivery solvent into the mass spectrometer which scanned from 100 to 1500 daltons. All compounds could be analyzed in the positive ESI mode, using 1:1 acetonitrile/water with 1% acetic acid as the delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2mM NH₄OAc in acetonitrile/water as delivery solvent.

Abbreviations: N-hydroxybenzotriazole (HOBT), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), N-methylmorpholine (NMM), 1-hydroxy-7-azabenzotriazole (HOAT), O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI).

EXAMPLE 1

This example illustrates the preparation of 5-nitro-2-(3-chloro-5-pyridyloxy)benzonitrile (1.1).



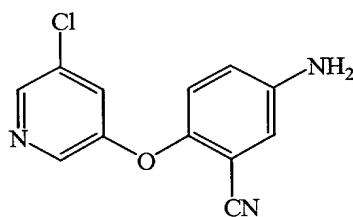
1.1

To a solution of 2-chloro-5-nitrobenzonitrile (18.3 g, 100 mmol) and 5-chloro 3-pyridinol (13 g, 100 mmol) in DMIF (100 mL) was added powdered K₂CO₃ (13.9 g, 100 mmol). After heating at 60°C for 12 hours, the suspension was poured into water (1 L). The resulting solid was collected by filtration, rinsed with water and dried under vacuum to afford 27.6 g (100%) of the title compound, mp 104-107 °C.

¹H NMR (400 MHz) (DMSO-*d*₆) δ 8.755 (d, *J*=2.8 Hz, 1H); 8.734 (br s, 1H); 8.576 (br s, 1H); 8.542 (dd, *J*=9.2, 2.7 Hz, 1H); 7.689 (t, *J*=2.2 Hz, 1H); 7.122 (d, *J*= 9.2 Hz, 1H).

EXAMPLE 2

This example illustrates the preparation of 5-amino-2-(3-chloro-5-pyridyloxy)benzonitrile (2.1).



2.1

5 To a vigorously stirred solution of the intermediate from Example 1 (6.23 g) in ethanol and THF was added a slurry of Raney Nickel (-300 mg, Aldrich). The flask was filled with H₂ at atmospheric pressure and the reduction was monitored by TLC. Starting material disappeared rapidly, to form a nitroso intermediate which gradually was converted to the desired aniline over about 5 hours. Stirring was stopped and Raney

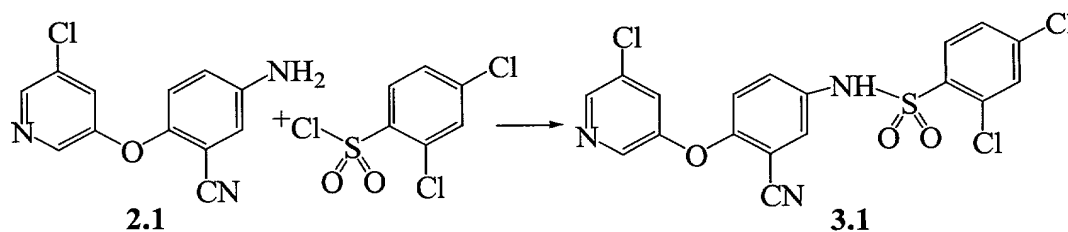
10 Nickel was attracted to the magnetic stirbar. The remaining solution was filtered through Celite® which was then rinsed with ethanol and methylene chloride. The combined organic portions were concentrated to provide 5.75 g of the product aniline as an oil which was used without further purification.

¹H NMR (400 MHz) (CDCl₃) δ 8.456 (d, *J*=1.9 Hz, 1H); 8.389 (d, *J*=2.6 Hz, 1H); 7.38 (m, 1H); 7.03 (m, 3H); 4.06 (m 2H).

15

EXAMPLE 3

This example illustrates the synthesis of 3.1.

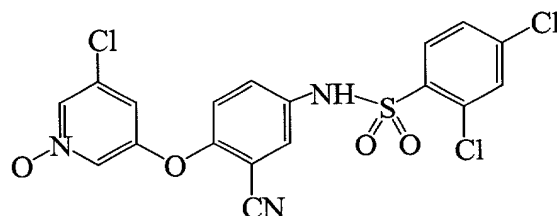


20 To a mixture of 5-amino-2-(3-chloro-5-pyridyloxy)benzonitrile from Example 2 (0.457 g) in methylene chloride was added 2,4-dichlorobenzenesulfonyl chloride (0.456 g, from Maybridge), followed by pyridine (150 μL). The reaction progress was monitored by TLC, and upon completion the solvent was removed under vacuum. The resulting residue was partitioned between methylene chloride and water.

25 The organic layer was drawn off and concentrated. The residue was triturated with ether to provide 0.447 g of the title compound as a white solid, mp 154-156 °C.

^1H NMR (400 MHz) (CDCl_3) δ 8.59 (s, 1H); 8.42 (s, 1H) 8.08 (d, $J=8.5$ Hz, 1H); 7.72(t, $J=1.8$, 1H); 7.605 (d, $J=2.7$ Hz, 1H) 7.53 (dd, $J=8.5$, 2 Hz, 1H); 7.48 (dd, $J=9.4$ Hz, 1H); 7.22 (s, 1H); 7.0 (d, $J=9.0$ Hz, 1H). m/e (M-H) 456.

The title compound was oxidized to the corresponding pyridine N-oxide using 3-chloroperoxybenzoic acid in methylene chloride to provide **3.2** as a white solid. m/e 470 (M+H).

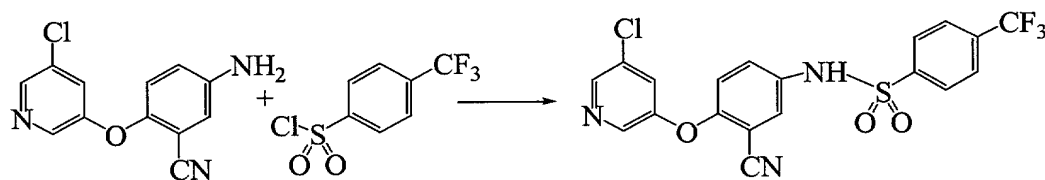


3.2

EXAMPLE 4

This example illustrates the synthesis of **4.1**.

10



2.1

4.1

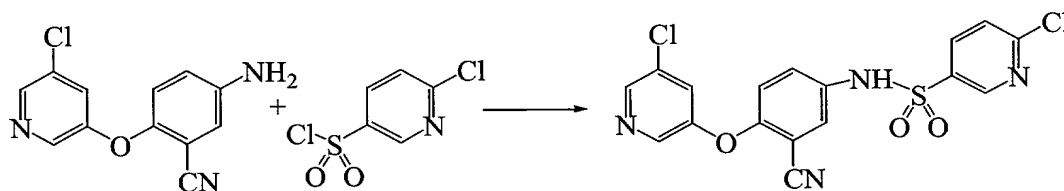
The title compound was prepared in a manner similar to Example 3, beginning with 1.6 g of the aniline of Example 2 and 1.6 g of 4-(trifluoromethyl)benzenesulfonyl chloride (from Maybridge). The crude product remaining after workup was purified by flash chromatography on silica eluting with 10% ethyl acetate / dichloromethane and then triturated in diethyl ether and collected as a white powder (1.04 g, 35% yield), mp 143-144 °C.

15

EXAMPLE 5

This example illustrates the synthesis of **5.1**.

20



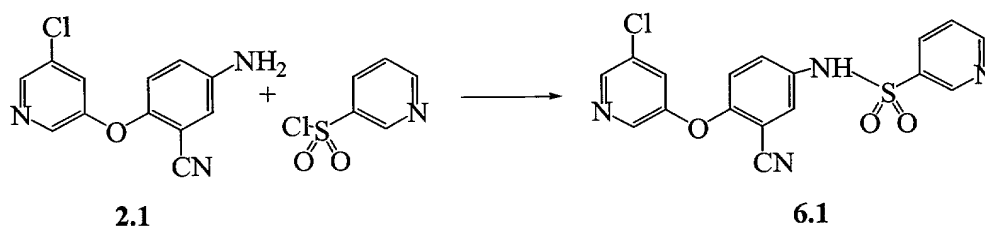
2.1

5.1

The title compound was prepared in a manner similar to Example 3, beginning with 397 mg of the aniline prepared as described in Example 2 and 345 mg of 2-chloropyridyl-5-sulfonyl chloride (prepared according to Hoffman, R.V., *Org Syn. Coll. Vol. VII*, p. 508-511). The crude product remaining after workup was purified by flash chromatography on silica eluting with 15% ethyl acetate / dichloromethane. The resulting solid was recrystallized from dichloromethane to provide the title compound (270 mg, 40%) as a white solid, m/e 419 (M-H).

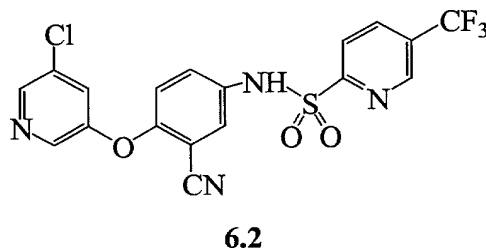
EXAMPLE 6

This example illustrates the synthesis of 6.1.



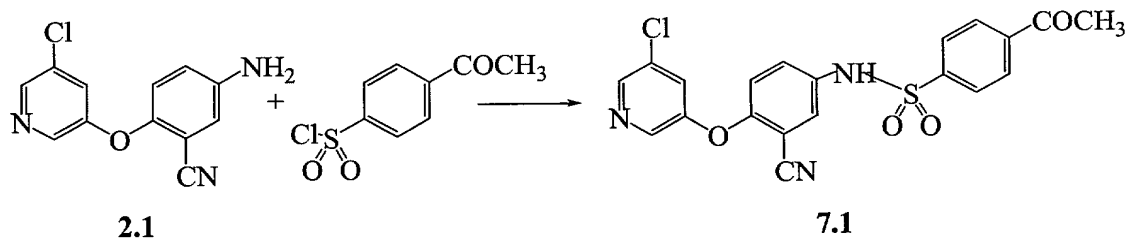
The title compound was prepared in a manner similar to Example 3, beginning with 400 mg of the aniline prepared as described in Example 2 and 349 mg of 3-pyridylsulfonyl chloride (prepared using methods similar to those described in *J. Med. Chem.* 40:1149 (1997)). The crude product remaining after workup was purified by flash chromatography on silica eluting with 1% ethanol / dichloromethane. The resulting solid was recrystallized from dichloromethane / diethyl ether and collected as a white solid (121 mg, 19%), mp 161-2 °C.

In a similar manner, 6.2 was prepared from aniline 2.1 and 5-trifluoromethyl-2-pyridinesulfonyl chloride, mp 174-176 °C.



EXAMPLE 7

This example illustrates the preparation of 7.1.

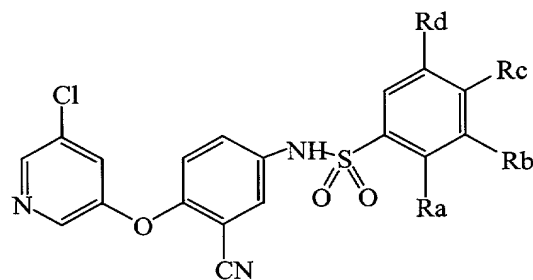


A round-bottomed flask was charged with the aniline prepared according to Example 2 (229 mg, 0.94 mmol), 4-acetylbenzenesulfonyl chloride (205 mg, 0.94 mmol, prepared according to Hoffman, R.V., Org. Syn. Coll. Vol. VII, p. 508-511), pyridine (75 mg, 0.94 mmol, Aldrich Chemical Co.), and a catalytic amount of DMAP (Aldrich Chemical Co.). Five mL of dichloromethane were added and the reaction was stirred at room temperature for eight hours. The reaction was then diluted with 25 mL of dichloromethane and washed successively with 10 mL of 1N HCl and brine. The organic portion was dried over MgSO₄ and passed through a plug of silica gel to remove baseline impurities. The resulting solid was triturated in hexanes to provide 362 mg (90%) of the title compound as a white solid.

¹H NMR (400MHz) (*d*₆-DMSO) δ 10.81 (1H, s); 8.52 (1H, d, *J*=1.8 Hz); 8.43 (1H, d, *J*=2.3 Hz); 8.11 (2H, dd, *J*=6.8 Hz, 2.0 Hz); 7.90 (2H, dd, *J*=6.8 Hz, 2.0 Hz); 7.85 (1H, dd, *J*=4.4 Hz, 2.2 Hz); 7.53 (1H, d, *J*=2.7 Hz); 7.35 (1H, dd, *J*=9.1 Hz, 2.8 Hz); 7.35 (1H, d, *J*=9.1 Hz); 2.61 (3H, s). MS ESI *m/e*: 425.8 (*M* - H).

The compounds provided in Table 1 were prepared using the methods described in Examples 1-7.

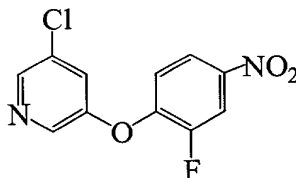
Table 1



	Ra	Rb	Rc	Rd	mp (°C)
7.2	Cl	H	Cl	CH ₃	181-182
7.3	H	H	OCF ₃	H	118-120
7.4	H	H	CN	H	160-163
7.5	H	H	SO ₂ CH ₃	H	174-175

EXAMPLE 8

This example illustrates the preparation of 3-fluoro-4-(3-chloro-5-pyridyloxy)nitrobenzene (**8.1**).



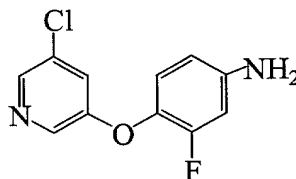
8.1

3,4-Difluoronitrobenzene (5.0 g, 32 mmol) and 5-chloro-3-pyridinol were combined using the procedure described in Example 1, to produce 8.2 g of the title compound.

¹H NMR (400 MHz) (DMSO-*d*₆) δ 8.562 (d, *J*=1.9 Hz, 1H); 8.537 (d, *J*=2.5 Hz, 1H); 8.384 (dd, *J*=10.8, 2.8 Hz, 1H); 8.117 (ddd, *J*=9.1, 2.7, 1.5 Hz, 1H); 7.967 (t, *J*=2.2 Hz, 1H); 7.418 (dd, *J*=9.2, 8.4 Hz, 1H).

EXAMPLE 9

This example illustrates the preparation of 3-fluoro-4-(3-chloro-5-pyridyloxy)aniline (**9.1**).



9.1

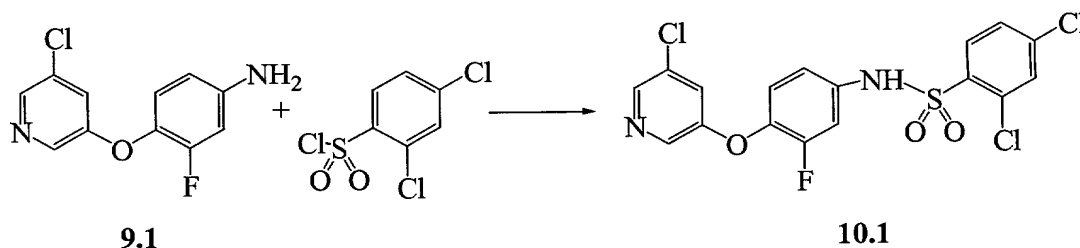
Using the method of Example 2, 3-fluoro-4-(3-chloro-5-pyridyloxy)nitrobenzene (**8.1**, 8.0 g) was converted to the title compound which was used directly in subsequent reactions.

MS (M + H) 239.1.

¹H NMR (400 MHz) (CDCl₃) δ 8.242 (br s, 2H); 7.142 (d, *J*=2.2 Hz, 1H); 6.937 (t, *J*=8.7 Hz, 1H); 6.512 (dd, *J*=12, 2.6 Hz, 1H); 6.444 (ddd, *J*=8.4, 2.7, 1.4 Hz, 1H); 3.62 (br s, 2H).

EXAMPLE 10

This example illustrates the preparation of 10.1.

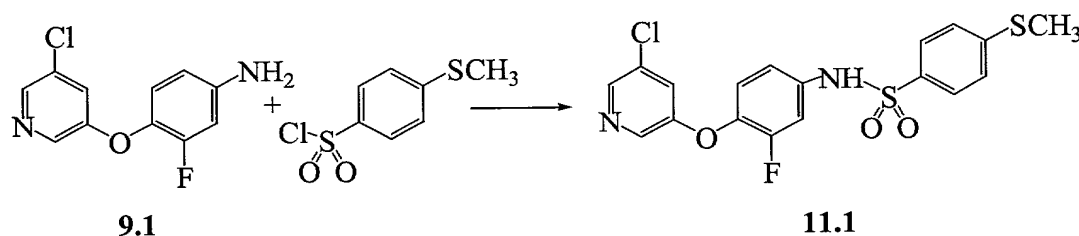


3-Fluoro-4-(3-chloro-5-pyridyloxy)aniline (239 mg, see Example 9) and
5 2,4-dichlorobenzenesulfonyl chloride (416 mg, Maybridge), were combined in a similar
manner to that described in Example 3. The crude product was purified by flash
chromatography on silica, eluting with 5% ethyl acetate / dichloromethane. The product
fractions were concentrated and the solid was recrystallized from diethyl ether / hexanes
to provide the title compound as a white solid (350 mg, 45%), mp 149-151 °C.

10

EXAMPLE 11

This example illustrates the preparation of 11.1.



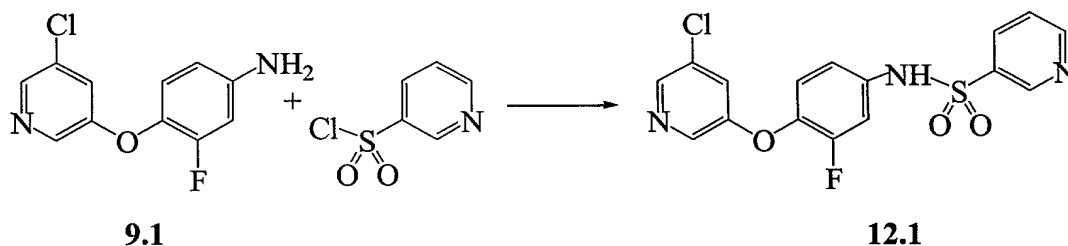
3-Fluoro-4-(3-chloro-5-pyridyloxy)aniline (310 mg, see Example 9) and 4-
15 methylthiobenzenesulfonyl chloride (298 mg, prepared as described in Burton, *et al.*, *J.*
Chem. Soc., 604-5 (1948)), were combined in a manner similar to that described in
Example 3. The crude product was purified by flash chromatography on silica, eluting
with ethyl acetate / hexanes / dichloromethane (1:5:4). The product fractions were
concentrated and the solid was recrystallized from hexanes / diethyl ether to provide the
20 title compound as a white solid (315 mg, 57%), mp 130-131 °C.

The title compound was oxidized with mCPBA to the corresponding
sulfoxide (11.2, mp 140-144 °C). The corresponding sulfone (11.3) was prepared using
4-(methylsulfonyl)benzenesulfonyl chloride (mp 165-168 °C).

EXAMPLE 12

25

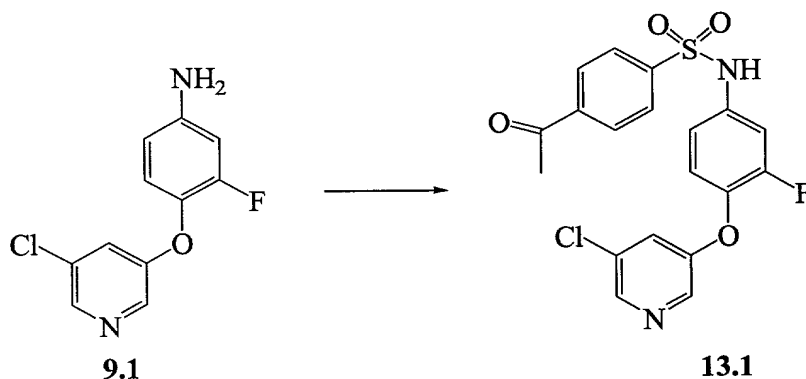
This example illustrates the preparation of 12.1.



The title compound was prepared in a manner similar to Example 3, beginning with 3-pyridylsulfonyl chloride (335 mg, see Example 6) and 3-fluoro-4-(3-chloro-5-pyridyloxy)aniline (310 mg, see Example 9) with the addition of a catalytic amount of 4-dimethylaminopyridine. When reaction was complete by TLC, the mixture was filtered to remove amine salts. The filtrate was concentrated and the residue was purified by flash chromatography on silica, eluting with 5% methanol / dichloromethane. The product fractions were combined, concentrated, and the residue was triturated with diethyl ether to provide the title compound as a white solid (221 mg, 32%), mp 129 °C.

EXAMPLE 13

This illustrates the synthesis of 5-(4-acetylbenzenesulfonamido-2-fluorophenoxy)-3-chloropyridine (13.1).



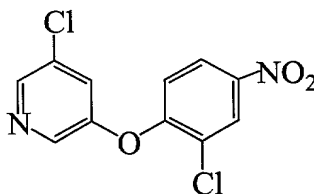
This was prepared using methods outlined in Examples 10-12, starting with 238 mg (1.0 mmol) of aniline 9.1, 218 mg (1.0 mmol) of 4-acetylbenzenesulfonyl chloride, 79 mg (1.0 mmol) of pyridine, catalytic DMAP, and 5 mL of methylene chloride. The title compound was obtained as a white solid (269 mg, 64%).

¹H NMR (400MHz) (*d*₆-DMSO) δ 10.75 (1H, d, *J*=4.7 Hz); 8.38 (1H, dd, *J*₁=4.8 Hz *J*₂=2.1 Hz); 8.26 (1H, dd, *J*₁=5.0 Hz *J*₂=2.4 Hz); 8.09 (2H, m); 7.91 (2H, m); 7.52 (1H, dd, *J*₁=4.7 Hz *J*₂=2.6 Hz); 7.21 (1H, dt, *J*₁=5 Hz *J*₂=1.0 Hz); 7.12 (1H, dd,

$J_1=12.2$ Hz $J_2=1.0$ Hz); 6.92 (1H, d, $J=8.8$ Hz); 2.59 (3H, t, $J=2.1$ Hz). MS ESI m/e: 418.7 (M - H).

EXAMPLE 14

5 This example illustrates the synthesis of 3-chloro-4-(3-chloro-5-pyridyloxy)nitrobenzene (14.1).



14.1

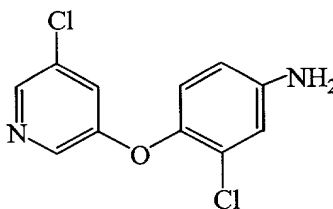
3-Chloro-4-fluoronitrobenzene (5.0 g, 28 mmol) and 5-chloro-3-pyridinol were combined using the procedure described in Example 1, to produce 7.9 g of the title compound.

^1H NMR (400 MHz) (DMSO- d_6) δ 8.571 (d, $J=2.0$ Hz, 1H); 8.509 (d, $J=2.4$ Hz, 1H); 8.499 (d, $J=2.7$ Hz, 1H); 8.208 (dd, $J=9.0, 2.7$ Hz, 1H); 7.949 (t, $J=2.3$ Hz, 1H); 7.335 (d, $J=9.1$ Hz, 1H).

15

EXAMPLE 15

This example illustrates the preparation of 3-chloro-4-(3-chloro-5-pyridyloxy)aniline (15.1).



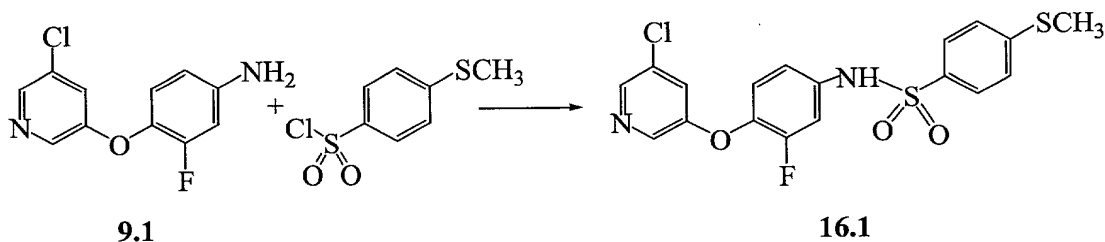
15.1

Using the method of Example 2, 3-chloro-4-(3-chloro-5-pyridyloxy)nitrobenzene (7.6 g) was converted to the title compound (7.2 g) and which was used directly in subsequent reactions.

^1H NMR (400 MHz) (CDCl $_3$) δ 8.244 (br s, 1H); 8.211 (br s, 1H); 7.096 (br s, 1H); 6.929 (d, $J=8.6$ Hz, 1H); 6.785 (d, $J=2.6$ Hz, 1H); 6.592 (dd, $J=8.6, 2.6$ Hz, 1H); 3.577 (br s, 2H). MS (M + H) 255.1.

EXAMPLE 16

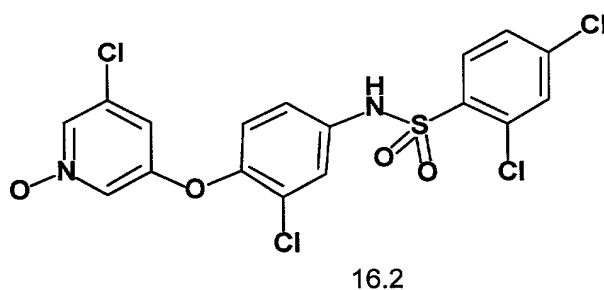
This example illustrates the preparation of 16.1.



5 3-Chloro-4-(3-chloro-5-pyridyloxy)aniline (410 mg, 15.1) and 2,4-dichlorobenzenesulfonyl chloride (390 mg, Maybridge), were combined in a similar manner to that described in Example 3. The crude product was purified by flash chromatography on silica, eluting with 5% ethyl acetate / dichloromethane. The product fractions were concentrated and the residue was triturated in hexanes to provide the title compound as a white solid (538 mg, 73%), mp 128-130 °C.

¹H NMR (400 MHz) (DMSO) δ 8.40 (d, *J*=1.8 Hz, 1H); 8.24 (d, *J*=2.4 Hz, 1H); 8.06 (d, *J*=8.5 Hz, 1H); 7.90 (d, *J*=2.0 Hz, 1H); 7.65 (dd, *J*=2, 8.5 Hz, 1H); 7.48 (t, *J*=2.2, 1H); 7.28 (d, *J*=2.5 Hz, 1H); 7.21 (d, *J*=8.84 Hz, 1H); 7.10 (dd, *J*=2.5, 7.1, 1H). MS *m/e* 465 (M+1).

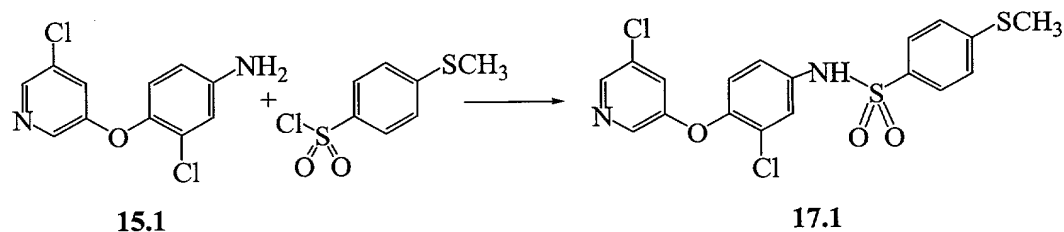
15 Compound 16.1 was oxidized with 3-chloroperoxybenzoic acid to produce the corresponding pyridine N-oxide, 16.2, as a white solid after trituration in diethyl ether, mp 205-207 °C.



EXAMPLE 17

This example illustrates the preparation of 17.1.

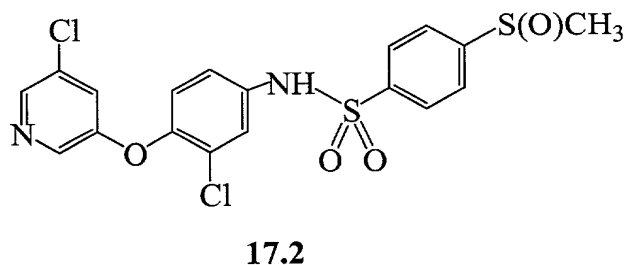
20



3-Chloro-4-(3-chloro-5-pyridyloxy)aniline (309 mg, 15.1) and 4-methylthiobenzenesulfonyl chloride (223 mg, prepared as described in Burton, *et al.*, .1. *Chem. Soc.*, 604-5 (1948)), were combined in a manner similar to that described in

- 5 Example 3. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate / hexanes / dichloromethane (1:5:4). The product fractions were concentrated and the residue obtained was triturated in hexanes to provide the title compound as a white solid (200 mg, 37%), mp 96-98 °C.

10 *Oxidation of 17.1 to sulfoxide 17.2*

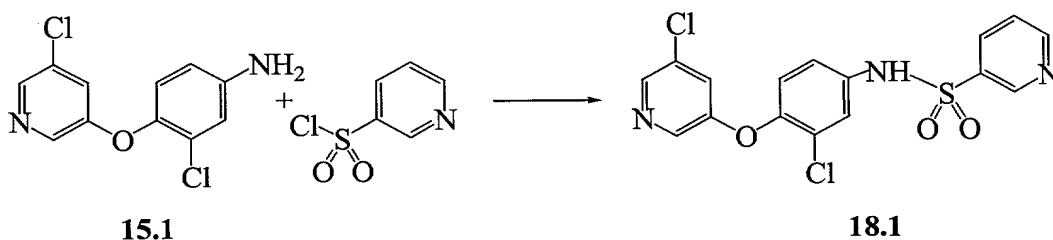


- Compound 17.1 was oxidized to the corresponding sulfoxide using Oxidation to sulfoxide potassium peroxymonosulfate in methanol and acetone. The reaction was monitored by TLC. After the reaction was complete, the mixture was filtered and the filtrate was washed with water, dried over MgSO₄, filtered and
- 15 concentrated. The residue was purified by chromatography on silica, eluting with 50% to 100% ethyl acetate / dichloromethane. Solvent was removed from the product fractions, and the residue was triturated in hexanes. The white solid product was collected by filtration to provide 121 mg of 17.2 (63%), mp 127-128 °C.

20

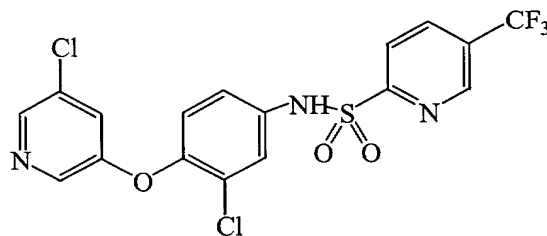
EXAMPLE 18

This example illustrates the preparation of 18.1.



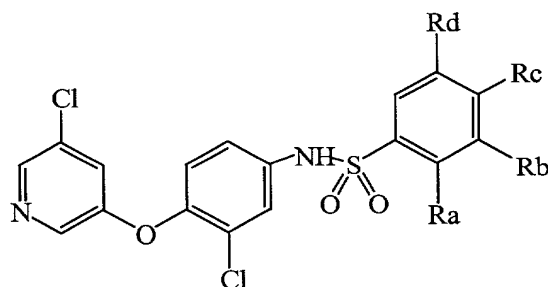
The title compound was prepared in a manner similar to Example 3, beginning with 3-pyridylsulfonyl chloride (335 mg, see Example 6) and 3-chloro-4-(3-chloro-5-pyridyloxy)aniline (411 mg, **15.1**) with the addition of a catalytic amount of 4-dimethylaminopyridine. When the reaction was completed by TLC, the mixture was filtered to remove amine salts. The filtrate was concentrated and the residue was purified by flash chromatography on silica, eluting with 5% methanol / dichloromethane. The product fractions were combined, concentrated, and the residue was triturated dichloromethane to provide the title compound as a white solid (149 mg, 22%), mp 164-165 °C.

In a similar manner, **18.2** (mp 174- 175 °C) was prepared from aniline **15.1** and 5-trifluoromethyl-2-pyridinesulfonyl chloride.



The compounds provided in Table 2 were prepared using commercially available intermediates and/or using the intermediates and methods described in the examples above.

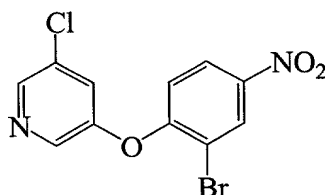
Table 2



	Ra	Rb	Rc	Rd	mp (°C) or m/e
18.3	H	H	CF ₃	H	172-174°C
18.4	Cl	H	CF ₃	H	111-113°C
18.5	H	H	COCH ₃	H	434.7
18.6	H	Cl	Cl	H	460.9

EXAMPLE 19

This example illustrates the preparation of 3-bromo-4-(3-chloro-5-pyridyloxy)nitrobenzene (19.1).



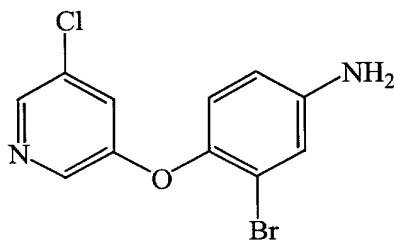
19.1

3-Bromo-4-fluoronitrobenzene (available from Reidel) and 5-chloro-3-pyridinol were combined using the procedure described in Example 1, to produce the title compound.

¹H NMR (400MHz, DMSO-*d*₆) δ 8.61 (d, J = 2.6 Hz, 1H), 8.57 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 2.5 Hz, 1H), 8.24 (dd, J = 9.3, 2.6 Hz, 1H), 7.94 (dd, J = 2.4, 2.2 Hz, 1H), 7.3 (d, J = 9.0 Hz, 2H). MS (EI): *m/z* 333 (25, M+H), 332 (15, M+H), 331 (100, M+H), 330 (10, M+H), 329 (76, M+H).

EXAMPLE 20

This example illustrates the preparation of 3-bromo-4-(3-chloro-5-pyridyloxy)aniline (20.1).



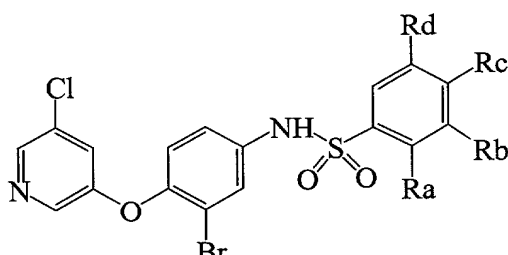
20.1

Using the method of Example 2, 3-bromo-4-(3-chloro-5-pyridyloxy)nitrobenzene (**19.1**) was converted to the title compound which was used directly in subsequent reactions.

¹H NMR (400MHz, DMSO-*d*₆) δ 8.32 (d, J = 2.1 Hz, 1H), 8.19 (d, J = 2.5 Hz, 1H), 7.28 (dd, J = 2.4, 2 Hz, 1H), 7.2 (d, J = 8.7 Hz, 1H), 6.9 (d, J = 2.6 Hz, 1H), 6.62 (dd, J = 8.7, 2.6 Hz, 1H). MS (EI): *m/e* 304 (5, M+H), 303 (35, M+H), 302 (20, M+H), 301 (100, M+H), 300 (15, M+H), 299 (90, M+H).

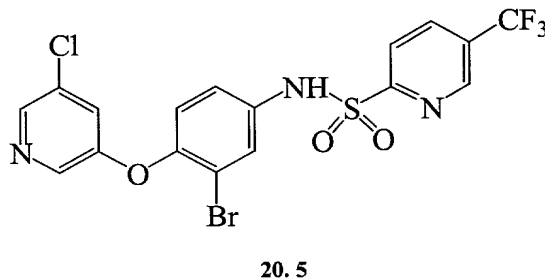
The compounds provided in Table 3 were prepared using **20.1** and commercially available intermediates and/or using the intermediates and methods described in the examples above.

Table 3



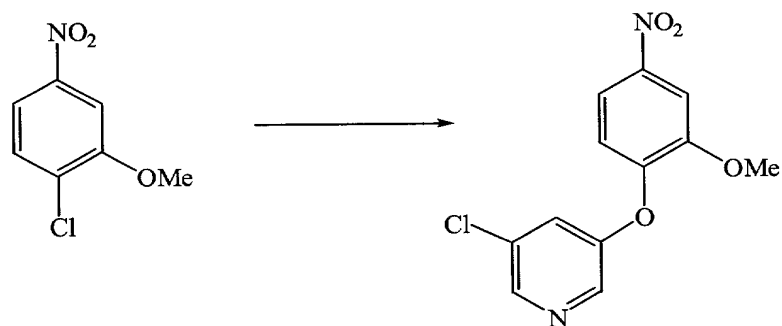
	R_a	R_b	R_c	R_d	mp (°C)
20.2	Cl	H	Cl	H	114-115
20.3	H	H	SCH ₃	H	160-162
20.4	H	H	S(O)CH ₃	H	169-171

Similarly, **20.5** was prepared from aniline **20.1** and 5-trifluoromethyl-2-pyridinesulfonyl chloride, mp 202-204 °C.



EXAMPLE 21

This example illustrates the preparation of 5-(4-nitro-2-methoxyphenoxy)-3-chloropyridine (**21.1**).



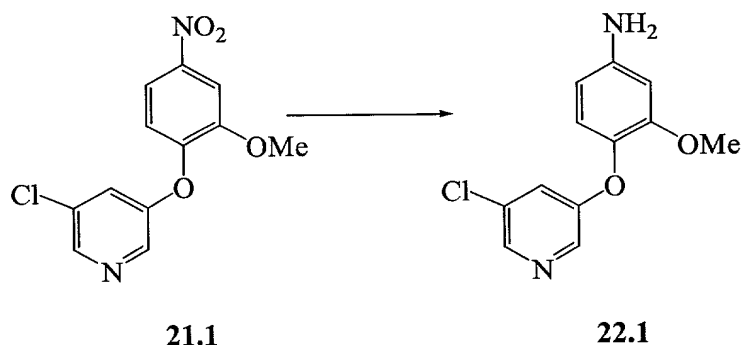
21.1

- 5 A round-bottomed flask was charged with 2-chloro-5-nitroanisole (1.03 g, 5.49 mmol, Avocado Chemical Co.), 5-chloro-3-pyridinol (750 mg, 5.76 mmol, Aldrich Chemical Co.), cesium carbonate (1.97 g, 6.04 mmol, Aldrich Chemical Co.), and anhydrous DMF (16 mL). The mixture was heated at 100 °C for 18 hours. The temperature was then increased to 130°C for an additional two hours, after which the
- 10 reaction was allowed to cool to room temperature. The reaction mixture was poured into 800 mL of distilled water, and extracted three times with 300 mL ethyl acetate. The combined extracts were dried over MgSO₄ and filtered. Solvent was removed from the filtrate under vacuum and the crude product was purified by flash chromatography on silica gel (5% hexanes in CH₂Cl₂ as eluant) to provide the title compound (1.42 g, 93%)
- 15 as a yellow solid.

MS ESI m/e: 281.1 (M + H).

EXAMPLE 22

This example illustrates the synthesis of 5-(4-amino-2-methoxyphenoxy)-3-chloropyridine (**22.1**).

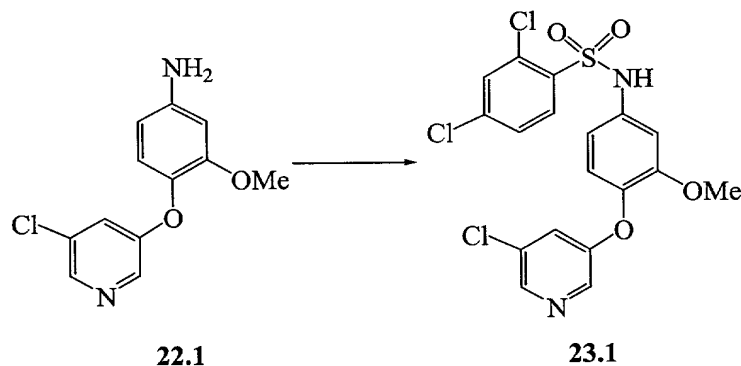


5 Using the method of Example 2, the nitro compound prepared in Example 21 (1.54 g, 6.56 mmol) was converted to 1.38 g (99%) of the title compound as an off-white solid. The product was used without further purification (upon standing several days in air the compound developed a very dark brown color).

MS ESI m/e: 251.1 (M + H).

EXAMPLE 23

This example illustrates the synthesis of 5-(4-(2,4-dichlorobenzenesulfonamido)-2-methoxyphenoxy)-3-chloropyridine (**23.1**).



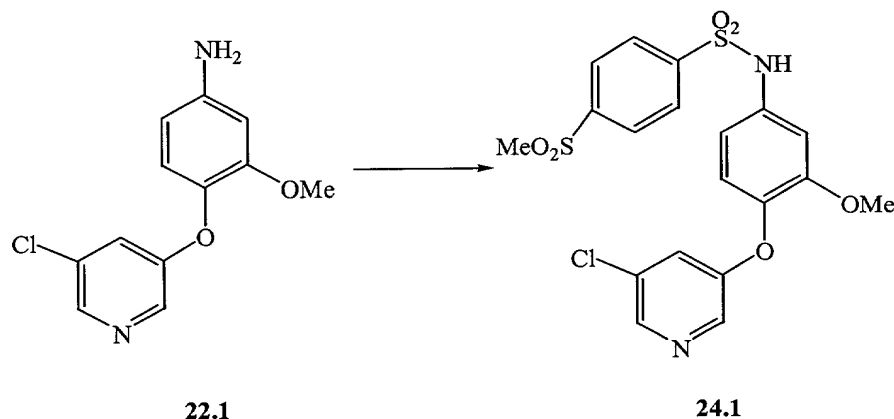
15 A round-bottomed flask was charged with aniline **22.1** (96 mg, 0.39 mmol), 2,4-dichlorobenzenesulfonyl chloride (104 mg, 0.42 mmol, Maybridge Chemical Co.), pyridine (28 mg, 0.39 mmol, Aldrich Chemical Co.), and a catalytic amount of DMAP (Aldrich Chemical Co.). Three mL of dichloromethane was added and the reaction mixture was stirred at room temperature for eight hours. The resulting mixture
20 was then diluted with 15 mL of dichloromethane and washed successively with 10 mL of 1N HCl and brine. The combined organic portions were dried over MgSO₄ then passed

through a plug of silica gel to remove baseline impurities. Solvent was removed from the filtrate and the resulting solid was triturated in hexanes to provide the title compound (69 mg, 40%) as a white powder.

$^1\text{H NMR}$ (400MHz) (d_6 -DMSO) δ 10.81 (1H, s); 8.29 (1H, d, $J=2.1$ Hz);
5 8.11 (1H, d, $J=2.4$ Hz); 8.07 (1H, d, $J=8.5$ Hz); 7.88 (1H, d, $J=2.0$ Hz); 7.63 (1H, dd, $J=8.7$ Hz, 2.1 Hz); 7.20 (1H, dd, $J=4.4$ Hz, 2.1 Hz); 7.07 (1H, d, $J=8.7$ Hz); 6.91 (1H, d, $J=2.4$ Hz); 6.68 (1H, dd, $J=8.7$ Hz, 2.5 Hz); 3.65 (3H, s). MS ESI m/e : 459.0 ($M + H$).

EXAMPLE 24

10 This example illustrates the synthesis of 5-(4-methylsulfonylbenzenesulfonamido-2-methoxyphenoxy)-3-chloropyridine (24.1).

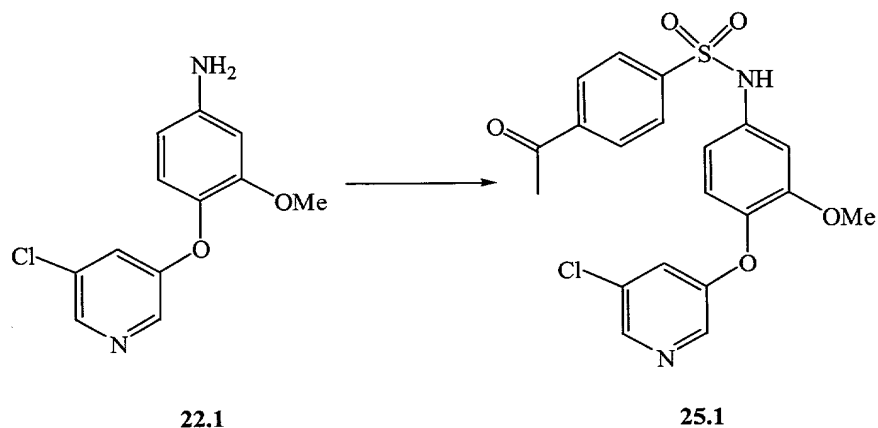


The title compound was prepared using the general procedure described in Example 22, starting with 150 mg (0.61 mmol) of the aniline, 155 mg (0.61 mmol, Aldrich Chemical Co.) of 4-methylsulfonebenzenesulfonyl chloride, 48 mg (0.61 mmol) of pyridine, catalytic DMAP, and 5 mL of methylene chloride. Following workup, the title compound was obtained (67 mg, 24%) as a white solid.

$^1\text{H NMR}$ (400MHz) (d_6 -DMSO) δ 10.63 (1H, s); 8.30 (1H, d, $J=2.0$ Hz);
15 8.14 (2H, m); 8.04 (1H, dd, $J=8.6$ Hz, 1.9 Hz); 7.27 (1H, dd, $J=4.5$ Hz, 2.2 Hz); 7.08 (1H, d, $J=8.6$ Hz); 6.93 (1H, d, $J=2.4$ Hz); 6.70 (1H, dd, $J=8.6$ Hz, 2.4 Hz); 3.67 (3H s); 3.28 (3H, s). MS ESI m/e : 467.0 ($M - H$).

EXAMPLE 25

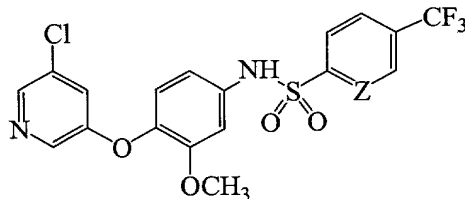
25 This example illustrates the synthesis of 5-(4-acetylbenzenesulfonamido-2-methoxyphenoxy)-3-chloropyridine (25.1).



The title compound was prepared using the procedure described in Example 7, starting with 82 mg (0.33 mmol) of aniline **22.1**, 72 mg (0.33 mmol) of 4-acetylbenzenesulfonyl chloride, 26 mg (0.33 mmol) of pyridine, catalytic DMAP, and 2 mL of methylene chloride. The title compound was produced (92 mg, 65%) as a white solid.

¹H NMR (400MHz) (*d*₆-DMSO) δ 10.52 (1H, s); 8.29 (1H, d, *J*=1.9 Hz); 8.10 (3H, m); 7.92 (2H, dd, *J*=8.0 Hz, 2.3 Hz); 7.23 (1H, dd, *J*=4.5 Hz, 2.4 Hz); 7.06 (1H, d, *J*=8.6 Hz); 6.93 (1H, dd, *J*=8.6 Hz, 2.4 Hz); 6.70 (1H, dd, *J*=8.6 Hz, 2.4 Hz); 3.65 (3H, s); 2.60 (3H, s). MS ESI *m/e*: 431.1 (*M* - H).

In a similar manner, **25.2** and **25.3** were prepared from aniline **22.1** and the appropriate sulfonyl chloride.

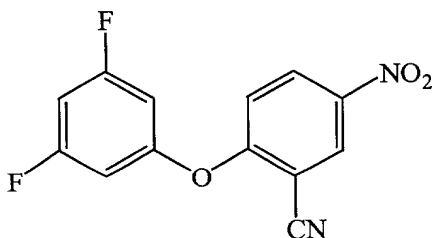


25.2 *Z* = N

25.3 *Z* = CH

EXAMPLE 26

This example illustrates the preparation of 5-nitro-2-(3,5-difluorophenoxy)-benzonitrile (**26.1**).

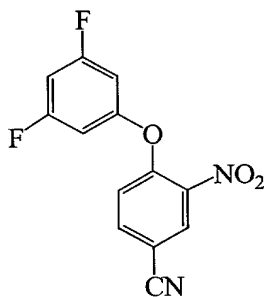


26.1

5 2-Chloro-5-nitrobenzonitrile (4.6 g, 25 mmol) and 3,5-difluorophenol were combined using the procedure described in Example 1, to produce 6.6 g of the title compound.

^1H NMR (400 MHz) (CDCl_3) δ 8.598 (d, $J=2.8$ Hz, 1H); 8.396 (ddd, $J=9.3, 2.8, 1.2$ Hz, 1H); 7.259 (d, $J=0.8$ Hz, 1H); 7.044 (d, $J=9.6$ Hz, 1H); 6.821 (m, 1H); 6.722 (m, 2H).

In a similar manner, 4-chloro-3-nitrobenzonitrile (4.6 g, 25 mmol) and 3,5-difluorophenol were combined to produce 6.9 g of 3-nitro-4-(3,5-difluorophenoxy)-benzonitrile (**26.2**), mp 132-136 °C.

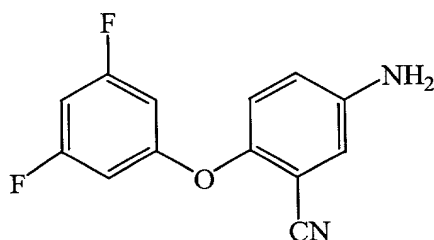


26.2

15 ^1H NMR (400 MHz) ($\text{DMSO}-d_6$) δ 8.72 (d, $J=2.0$ Hz, 1H); 8.165 (dd, $J=8.8, 1.9$ Hz, 1H); 7.422 (d, $J=8.8$ Hz, 1H); 7.227 (m, 1H); 7.103 (m, 2H).

EXAMPLE 27

20 This example illustrates the preparation of 5-amino-2-(3,5-difluorophenoxy)benzonitrile (**27.1**).

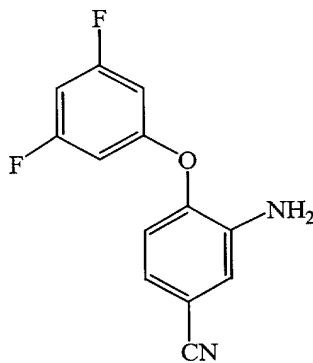


27.1

Using the method of Example 2, 5-nitro-2-(3,5-difluorophenoxy)-benzonitrile (26.1, 6.6 g) was converted to the title compound (5.47 g, mp 80-84°C) which was used directly in subsequent reactions.

- 5 $^1\text{H NMR}$ (400 MHz) (TFA/DMSO- d_6) δ 11.2 (br s, 2H); 7.083 (d, $J=9.2$ Hz, 1H); 7.077 (d, $J=2.8$ Hz, 1H); 7.033 (dd, $J=9.2, 2.4$ Hz, 1H); 6.998 (tt, $J=9.2, 2.4$ Hz, 1H); 6.727 (dd, $J=8.4, 2.0$ Hz, 2H).

Similarly, 3-amino-4-(3,5-difluorophenoxy)benzonitrile (27.2) was prepared from 26.2.



27.2

- 10 $^1\text{H NMR}$ (400 MHz) (DMSO- d_6) δ 7.14 (d, $J=2.0$ Hz, 1H); 7.03-6.96 (m, 3H); 6.70 (dd, $J=8.6, 2.3$ Hz, 2H); 5.60 (s, 2H).

- The compounds provided in Table 4 were prepared using 27.1 and commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.
- 15

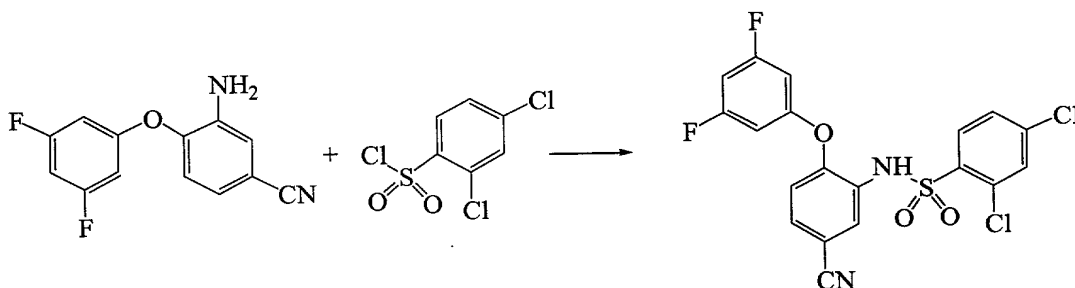
Table 4

	Ra	Rb	Rc	Rd	mp(°C) or m/e
27.3	Cl	H	Cl	H	452.7
27.4	H	H	OCH ₃	H	414.8
27.5	H	H	I	H	510.6
27.6	H	H	C(O)CH ₃	H	482.7
27.7	H	H	CF ₃	H	141-144 °C

EXAMPLE 28

5

This example illustrates the preparation of 28.1.

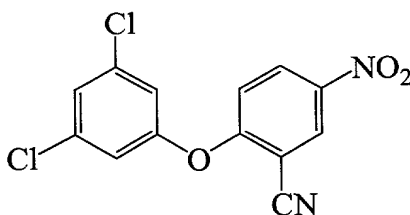


28.1

3-Amino-4-(3,5-difluorophenoxy)benzonitrile (201 mg, 27.2) and 2,4-dichlorobenzenesulfonyl chloride (302 mg, Maybridge), were combined in a similar manner to that described in Example 3, then heated to 40 °C. The crude product obtained after workup was purified by flash chromatography on silica, eluting with dichloromethane. The product fractions were concentrated and the residue was triturated with diethyl ether to provide the title compound as a white solid (150 mg, 37%), mp 197-200 °C.

EXAMPLE 29

This example illustrates the preparation of 5-nitro-2-(3,5-dichlorophenoxy)-benzonitrile (**29.1**).



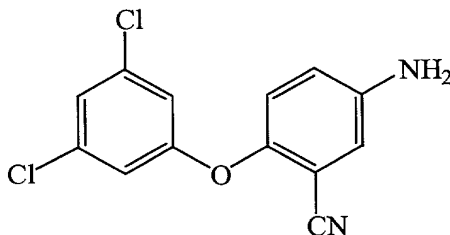
29.1

5 2-Chloro-5-nitrobenzonitrile (0.9 g, 5 mmol) and 3,5-dichlorophenol were combined using the procedure described in Example 1, to produce 1.5 g of the title compound, mp 188-190 °C.

¹H NMR (400 MHz) (CDCl₃) δ 8.597 (d, *J*=2.4 Hz, 1H); 8.397 (ddd, *J*=9.2, 2.8, 0.8 Hz, 1H); 7.360 (dd, *J*=3.2, 2.0 Hz, 1H); 7.089 (dd, *J*=1.6, 0.8 Hz, 2H)
10 7.008 (d, *J*=9.6 Hz, 1H).

EXAMPLE 30

This example illustrates the preparation of 5-amino-2-(3,5-dichlorophenoxy)benzonitrile (**30.1**).

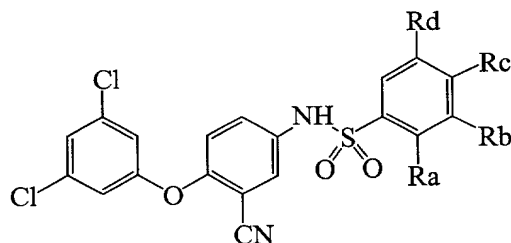


30.1

15 To a solution of 5-nitro-2-(3,5-dichlorophenoxy)benzonitrile (**29.1**, 1.5 g) in ethyl acetate (45 mL) was added stannous chloride dihydrate (5.47 g). The mixture was heated to 85°C for 30 minutes during which time a thick white precipitate formed. The reaction vessel was cooled and the mixture was treated with 100 mL of 0.5 N NaGH.
20 The resulting mixture was extracted twice with ethyl acetate. The combined organic extracts were dried over MgSO₄ and concentrated under vacuum to afford the title compound which was used without further purification. MS *m/e* 279 (M+H).

The compounds provided in Table 5 were prepared using 30.1 and commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

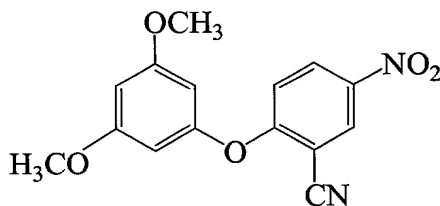
Table 5



	Ra	Rb	Rc	Rd	mp (°C)
30.2	Cl	H	Cl	H	143-144
30.3	H	H	CF ₃	H	148-149

EXAMPLE 31

This example illustrates the preparation of 5-nitro-2-(3,5-dimethoxyphenoxy)benzonitrile (31.1).



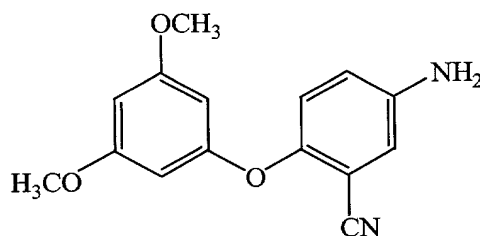
31.1

2-Chloro-5-nitrobenzonitrile (5.3 g) and 3,5-dimethoxyphenol (4.5 g, Aldrich) were combined using the procedure described in Example 1, to produce the title compound as a brown solid.

¹H NMR (400 MHz) (DMSO) δ 8.84 (d, *J*=2.8, 1H); 8.44 (dd, *J*=9.3, 2.8 Hz, 1H); 7.07 (d, *J*=9.3 Hz, 1H); 6.51 (s, 3H); 3.76 (s, 6H).

EXAMPLE 32

This example illustrates the preparation of 5-amino-2-(3,5-dimethoxyphenoxy)benzonitrile (**32.1**).



32.1

To a solution of 5-nitro-2-(3,5-dichlorophenoxy)benzonitrile (**31.1**, 8.76 g) in ethyl acetate was added tin chloride (33 g). The mixture was heated to reflux for one hour. The resulting mixture was cooled and 0.5 N sodium hydroxide solution was added to induce the precipitation of tin salts which were removed by filtration. The filtrate was concentrated to provide 7.5 g of the title compound as an orange solid which was used in subsequent reactions without purification.

$^1\text{H NMR}$ (400 MHz) ($\text{DMSO}-d_6$) δ 6.95-6.87 (m, 3H); 6.25 (t, $J=2.2$ Hz, 1H); 6.04 (d, $J=2.2$ Hz, 2H); 5.49 (s, 2H); 3.70 (s, 6H).

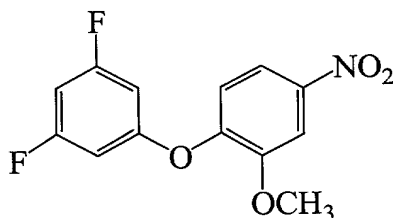
The compounds provided in Table 6 were prepared using **32.1** and commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

Table 6

	Ra	Rb	Rc	Rd	mp (°C) or m/e
32.2	Cl	H	Cl	H	477
32.3	Cl	H	CF ₃	H	101-105°C
32.4	H	H	I	H	439
32.5	H	H	OCH ₃	H	162-164°C

EXAMPLE 33

This example illustrates the preparation of 3-methoxy-4-(3,5-difluorophenoxy)-nitrobenzene (**33.1**).

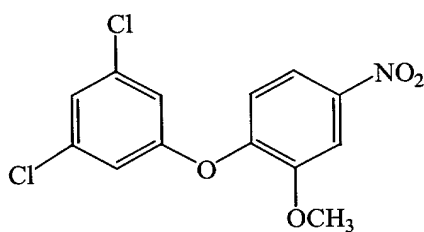


33.1

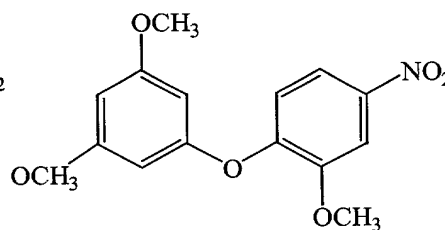
4-Chloro-3-methoxynitrobenzene (2.64 g) and 3,5-difluorophenol (Aldrich) were combined using the procedure described in Example 1 and heated to 125°C, to produce the title compound as a thick brown oil which solidified on trituration with hexane/methanol to yield 1.33 g of **33.1** as a red solid.

¹H NMR (400 MHz) (DMSO-*d*₆) δ 7.963 (d, *J*=2.6 Hz, 1H); 7.903 (dd, *J*=8.8, 2.7 Hz, 1H); 7.316 (d, *J*=8.8 Hz, 1H); 7.035 (m, 1H); 6.796 (m, 2H); 3.909 (s, 3H).

In a similar manner, 3-methoxy-4-(3,5-dichlorophenoxy)nitrobenzene (**33.2**) and 3-methoxy-4-(3,5-dimethoxyphenoxy)nitrobenzene (**33.3**) were prepared beginning with 3,5-dichlorophenol and 3,5-dimethoxyphenol, respectively.



33.2



33.3

33.2 3-methoxy-4-(3,5-dichlorophenoxy)nitrobenzene

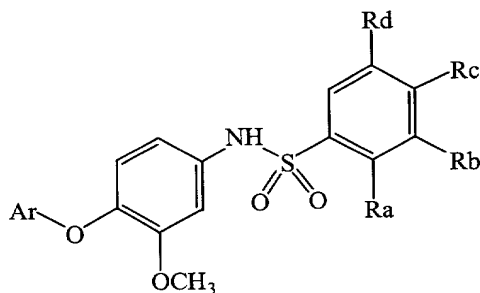
¹H NMR (400 MHz) (DMSO-*d*₆) δ 7.960 (d, *J*=2.6 Hz, 1H); 7.900 (dd, *J*=8.9, 2.7 Hz, 1H); 7.394 (t, *J*=1.7 Hz, 1H); 7.310 (d, *J*=8.8 Hz, 1H); 7.107 (t, *J*=1.4 Hz, 2H); 3.907 (s, 3H).

33.3 3-methoxy-4-(3,5-dimethoxyphenoxy)nitrobenzene

^1H NMR (400 MHz) ($\text{DMSO}-d_6$) δ 7.910 (d, $J=2.6$ Hz, 1H); 7.862 (dd, $J=8.8, 2.6$ Hz, 1H); 7.064 (d, $J=8.8$ Hz, 1H); 6.353 (t, $J=2.2$ Hz, 1H); 6.207 (d, $J=2.2$ Hz, 2H); 3.927(s, 3H); 3.716 (s, 6H).

Each of the nitrobenzene derivatives (**33.1**, **33.2** and **33.3**) were reduced to the corresponding aniline derivative using the Raney nickel procedure of Example 2. The aniline derivatives were then converted to the compounds shown in Table 7 using commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

Table 7

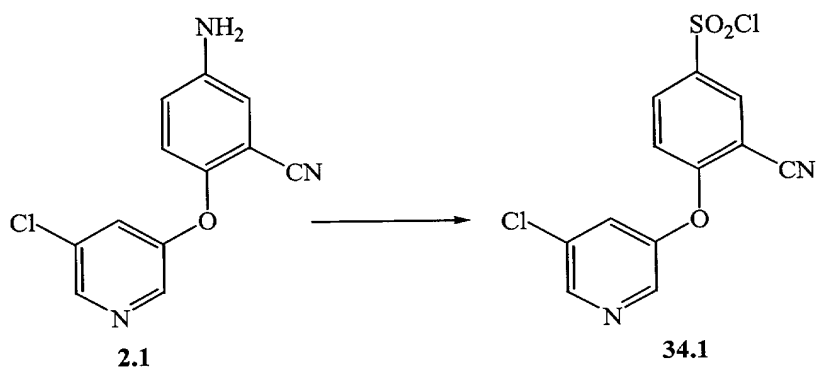


10

	Ar	Ra	Rb	Rc	Rd	mp(°C)
33.4	3,5-dichlorophenyl	Cl	H	Cl	H	128-131
33.5	3,5-difluorophenyl	H	H	CF ₃	H	141-143
33.6	3,5-dichlorophenyl	H	H	CF ₃	H	165-166
33.7	3,5-difluorophenyl	Cl	H	Cl	H	120-124
33.8	3,5-difluorophenyl	H	H	OCH ₃	H	129-133
33.9	3,5-dimethoxyphenyl	Cl	H	Cl	H	100-103
33.10	3,5-dimethoxyphenyl	Cl	H	CF ₃	H	72-79
33.11	3,5-dimethoxyphenyl	H	H	OCH ₃	H	92-95

EXAMPLE 34

This example illustrates the synthesis of 5-(4-chlorosulfonyl-2-cyanophenoxy)-3-chloropyridine (**34.1**).

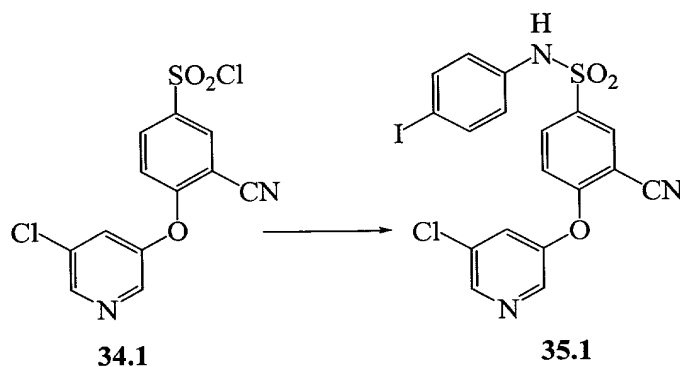


Aniline **2.1** (3.11 g, 12.69 mmol) was converted to the corresponding sulfonyl chloride according to the procedure of R. V. Hoffman (*Org. Syn. Coll. Vol.*, VII, 508-511), yielding 770 mg (18%) of **34.1** as a white solid.

5 MS ESI m/e: 331.0 (M + H)

EXAMPLE 35

This example illustrates the synthesis of compound **35.1**.



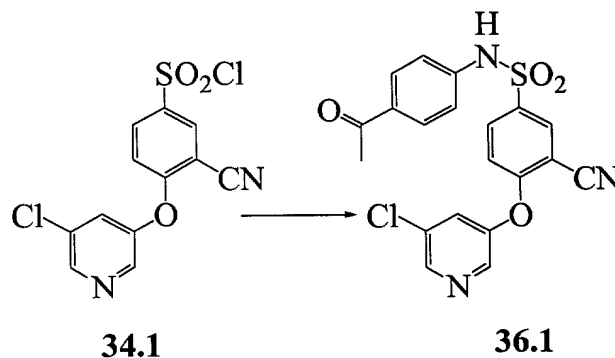
10 The title compound was prepared using the method described in Example 3, starting with 4-iodoaniline (136 mg, 0.6197 mmol, Aldrich Chemical Co.), 5-(4-chlorosulfonyl-2-cyanophenoxy)-3-chloropyridine (136 mg, 0.4131 mmol, **34.1**), pyridine (49 mg, 0.6197 mmol), catalytic DMAP, and 3 mL of methylene chloride. The product was obtained as a white solid (187 mg, 89%).

15 $^1\text{H NMR}$ (400MHz) (d_6 -DMSO) δ 10.57 (1H, s); 8.62 (1H, d, $J=1.8$ Hz); 8.60 (1H, d, $J=2.2$ Hz); 8.28 (1H, d, $J=2.4$ Hz); 8.12 (1H, d, $J=2.2$ Hz); 7.93 (1H, dd, $J_1=8.9$ Hz $J_2=2.3$ Hz); 7.61 (2H, dd, $J_1=8.8$ Hz $J_2=2.0$ Hz); 7.17 (1H, d, $J=9.0$); 6.93 (2H, dd, $J_1=8.8$ Hz $J_2=2.0$ Hz). MS ESI m/e: 509.9 (M - H).

20

EXAMPLE 36

This example illustrates the synthesis of compound **36.1**.

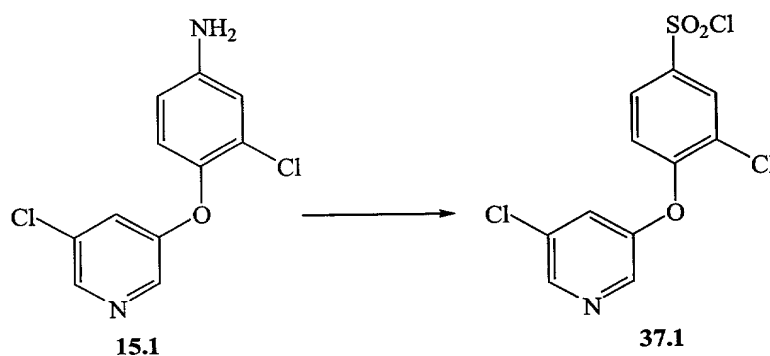


The title compound was prepared using the method described in Example 35, starting with 4-acetylaniline (100 mg, 0.31 mmol, Aldrich Chemical Co.), 5-(4-chlorosulfonyl-2-cyanophenoxy)-3-chloropyridine (62 mg, 0.46 mmol), pyridine (36 mg, 0.46 mmol), catalytic DMAP, and 3 mL of methylene chloride. The title compound 36.1 was obtained as a white solid (120 mg, 92%).

^1H NMR (400MHz) (d_6 -DMSO) δ 10.53 (1H, s); 8.58 (1H, d, $J=1.9$ Hz); 8.53 (1H, d, $J=2.4$ Hz); 8.15 (1H, d, $J=2.5$ Hz); 7.99 (1H, dd, $J_1=4.4$ Hz $J_2=2.2$ Hz); 7.86 (1H, dd, $J_1=8.8$ Hz $J_2=2.5$ Hz); 7.59 (2H, dd, $J_1=8.8$ Hz $J_2=2.0$ Hz); 7.13 (1H, d, $J=8.7$ Hz); 6.93 (2H, dd, $J_1=8.8$ Hz $J_2=2.0$ Hz); 2.61 (1H, s). MS ESI m/e : 425.9 (M - H).

EXAMPLE 37

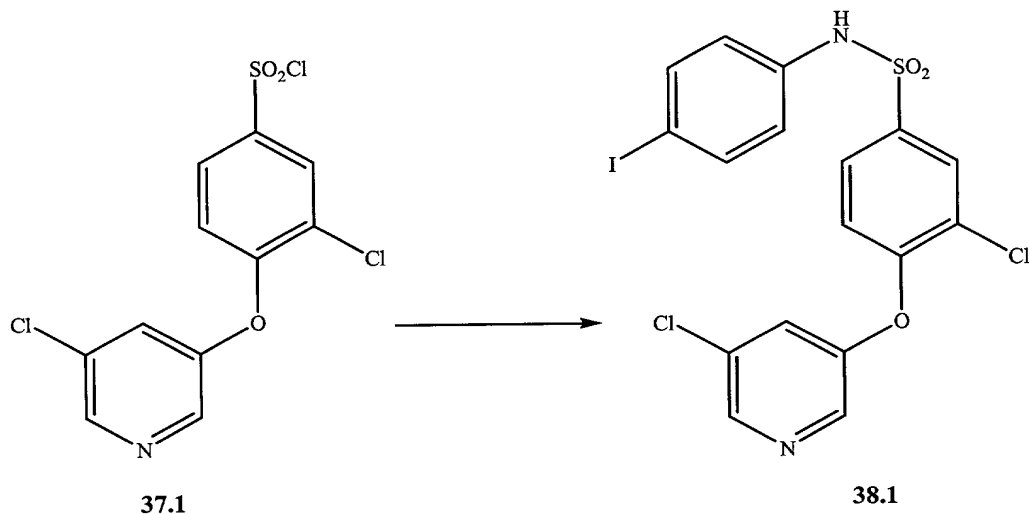
This example illustrates the synthesis of 5-(4-chlorosulfonyl-2-chlorophenoxy)-3-chloropyridine (37.1).



Aniline 15.1 (2.10 g, 8.24 mmol) was converted to the corresponding sulfonyl chloride 37.1, according to the procedure of R. V. Hoffman (Org. Syn. Coll. Vol., VII, 508-511). The title compound was obtained as a slightly yellow solid (1.65 g, 59%) MS ESI m/e : 338.0 (M + H).

EXAMPLE 38

This example illustrates the synthesis of compound **38.1**.

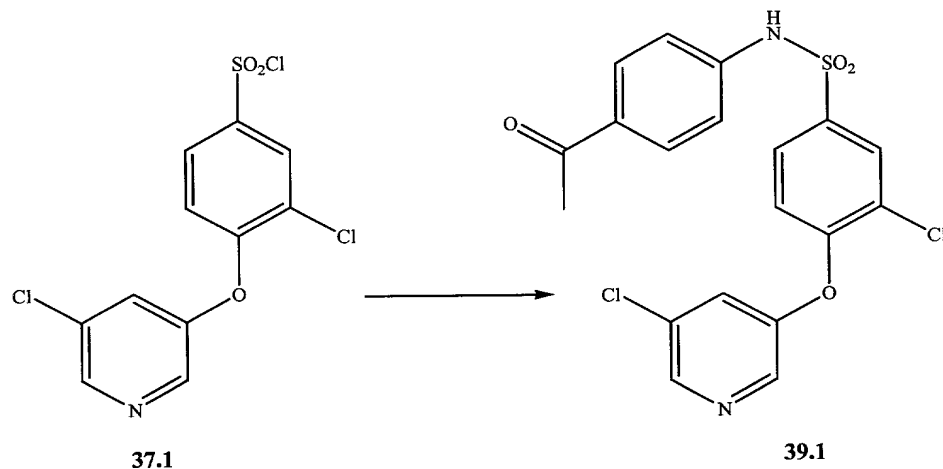


- 5 The title compound was prepared using the method described in Example 35, starting with 4-iodoaniline (101 mg, 0.46 mmol), S-(4-chlorosulfonyl-2-chlorophenoxy)-3-chloropyridine (104 mg, 0.31 mmol), pyridine (35 mg, 0.46 mmol), catalytic DMAP, and 3 mL of methylene chloride. Compound **38.1** was obtained as a white solid (150 mg, 94%).

10 $^1\text{H NMR}$ (400MHz) (d_6 -DMSO) δ 10.50 (1H, s); 8.55 (1H, d, $J=2.1$ Hz); 8.45 (1H, d, $J=2.5$ Hz); 7.93 (1H, d, $J=2.2$ Hz); 7.89 (1H, dd, $J_1=4.4$ Hz $J_2=2.2$ Hz); 7.67 (1H, dd, $J_1=8.7$ Hz $J_2=2.2$ Hz); 7.61 (2H, dd, $J_1=8.8$ Hz $J_2=2.0$ Hz); 7.22 (1H, d, $J=8.7$ Hz); 6.94 (2H, dd, $J_1=8.8$ Hz $J_2=2.0$ Hz). MS ESI m/e : 518.9 (M - H).

EXAMPLE 39

- 15 This example illustrates the synthesis of compound **39.1**.

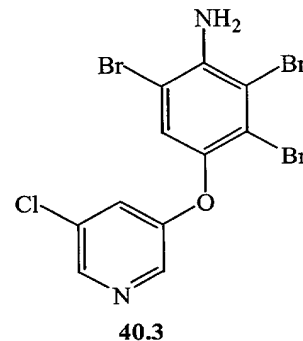
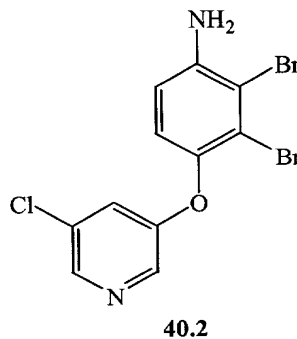
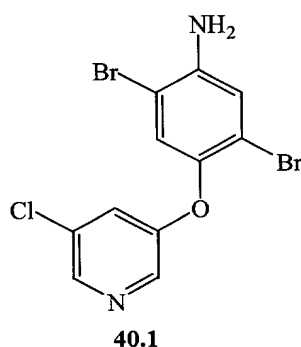


The title compound was prepared using the method of Example 38, starting with 4-acetylaniline (55 mg, 0.41 mmol), 5-(4-chlorosulfonyl-2-chlorophenoxy)-3-chloropyridine (92 mg, 0.27 mmol), pyridine (33 mg, 0.41 mmol), catalytic DMAP, and 3 mL of inethylene chloride. After workup, **39.1** was obtained as a white solid (130 mg, 93%).

^1H NMR (400MHz) (d_6 -DMSO) δ 10.94 (1H, s); 8.54 (1H, d, $J=2.0$ Hz); 8.44 (1H, d, $J=2.2$ Hz); 8.01 (1H, d, $J=2.1$ Hz); 7.90 (1H, dd, $J_1=4.4$ Hz $J_2=2.2$ Hz); 7.86 (2H, dd, $J_1=8.8$ Hz $J_2=1.6$ Hz); 7.75 (1H, dd, $J_1=8.7$ Hz $J_2=2.2$ Hz); 7.23 (3H, m). MS ESI m/e : 435.0 (M - H).

EXAMPLE 40

This example illustrates the preparation of 5-(4-amino-2,5-dibromophenoxy)3-chloropyridine (**40.1**), 5-(4-amino-2,3 -dibromophenoxy)-3-chloropyridine (**40.2**), and 5-(4-amino-2,3,5-tribromophenoxy)-3-chloropyridine (**40.3**).



To a 0.1 M solution of 3-bromo-4-(3-chloro-5-pyridyloxy)aniline (**20.1**) in acetic acid was added bromine (Aldrich). The resulting solution was stirred for two days. Most of the acetic acid was removed azeotropically using hexanes and the residue was adjusted to pH 6 using 4 M aqueous NaOH. The aqueous layer was extracted with ethyl acetate and the combined organic portions were washed with brine (2X), dried over sodium sulfate, filtered and concentrated under reduced pressure. The products were separated by chromatography to provide 5-(4-amino-2,5 -dibromophenoxy)-3-chloropyridine (**40.1**, 32%), 5-(4-amino-2,3-dibromophenoxy)-3-chloropyridine (**40.2**, 15%), and 5-(4-amino-2,3,5-tribromophenoxy)-3-chloropyridine (**40.3**, 13%).

40.1: ^1H NMR (400MHz, DMSO- d_6) δ 8.35 (d, $J = 1.5$ Hz, 1H), 8.22 (d, $J = 2.5$ Hz, 1H), 7.46 (d, $J = 1.0$ Hz, 1H), 7.39 (dd, $J = 2.8, 2.6$ Hz, 1H), 7.14 (s, 1H), 5.6 (s,

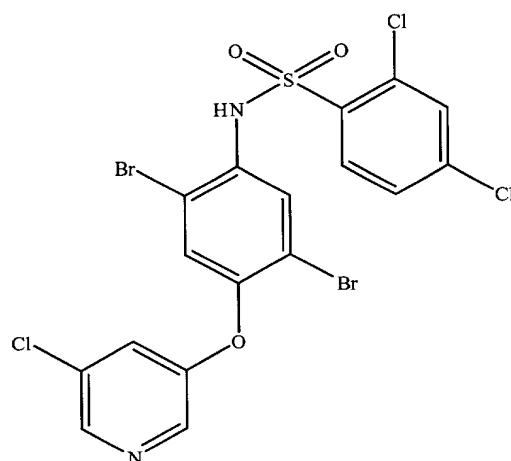
2H). MS (EI): m/z 383 (18, M+H), 382 (10, M+H), 381 (75, M+H), 380 (15, M+H), 379 (100, M+H), 378 (7, M+H), 377 (50, M+H).

40.2: ^1H NMR (400MHz, DMSO- d_6) δ 8.34 (d, J = 2 Hz, 1H), 8.21 (d, J = 2.6 Hz, 1H), 7.36 (dd, J = 2.4, 2.2 Hz, 1H), 7.32 (dd, J = 8.8 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 5.7 (s, 2H). MS (EI): m/z 383 (18, M+H), 382 (10, M+H), 381 (75, M+H), 380 (15, M+H), 379 (100, M+H), 378 (7, M+H), 377 (50, M+H).

40.3: ^1H NMR (400MHz, DMSO- d_6) δ 8.36 (d, J = 2.2 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 7.63 (s, 1H), 7.48 (dd, J = 2.4, 1.9 Hz, 1H), 5.65 (s, 2H). MS (EI): m/z 463 (10, M+H), 462 (5, M+H), 461 (50, M+H), 460 (12, M+H), 459 (100, M+H), 458 (12, M+H), 457 (85, M+H), 456 (5, M+H), 455 (25, M+H).

EXAMPLE 41

This example illustrates the preparation of 5-(4-(2,4-dichlorobenzene-sulfonamido)-2,5-dibromophenoxy)-3-chloropyridine (**41.1**).



15

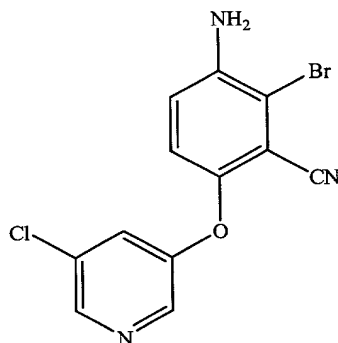
41.1

5-(4-(2,4-dichlorobenzene-sulfonamido)-2,5-dibromophenoxy)-3-chloropyridine was prepared in 39% yield from **40.1** and 2,4-dichlorobenzene-sulfonyl chloride using the method of Example 3.

^1H NMR (400MHz, DMSO- d_6) δ 10.6 (s, 1H), 8.47 (bs, 1H), 8.33 (bs, 1H), 7.9 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.68 (bs, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.57 (s, 1H), 7.52 (s, 1H). MS (EI): m/z 593 (6, M+H), 592 (4, M+H), 591 (27, M+H), 590 (10, M+H), 589 (50, M+H), 588 (10, M+H), 587 (45, M+H), 586 (3, M+H), 585 (17, M+H).

EXAMPLE 42

This example illustrates the preparation of 5-(4-amino-2-cyano-3-bromophenoxy)-3-chloropyridine (**42.1**).



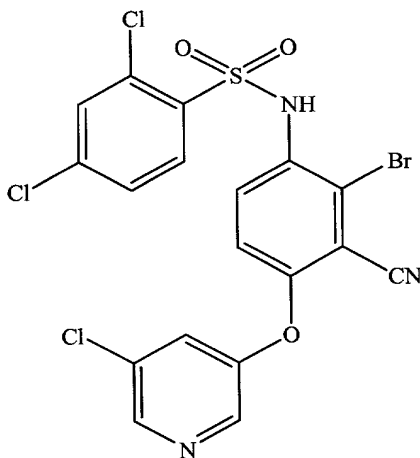
42.1

- 5 3-Cyano-4-(3-chloro-5-pyridyloxy)aniline (see Example 2) was combined with bromine in acetic acid in a manner similar to that described in Example 40 to produce 5-(4-amino-2-cyano-3-bromophenoxy)-3-chloropyridine (37%) after chromatography.

10 $^1\text{H NMR}$ (400MHz, $\text{DMSO}-d_6$) δ 8.44 (d, $J = 1.8$ Hz, 1H), 8.37 (d, $J = 2.2$ Hz, 1H), 7.7 (dd, $J = 2.2, 1.8$ Hz, 1H), 7.13 (1/2ABq, $J = 9.1$ Hz, 1H), 7.11 (1/2ABq, $J = 9.1$ Hz, 1H), 5.83 (s, 2H). MS (EI): m/z 328 (30, $\text{M}+\text{H}$), 327 (13, $\text{M}+\text{H}$), 326 (100, $\text{M}+\text{H}$), 325 (10, $\text{M}+\text{H}$), 324 (75, $\text{M}+\text{H}$).

EXAMPLE 43

- 15 This example illustrates the synthesis of 5-(4-(2,4-dichlorobenzene-sulfonamido)-2-cyano-3-bromophenoxy)-3-chloropyridine (**43.1**).



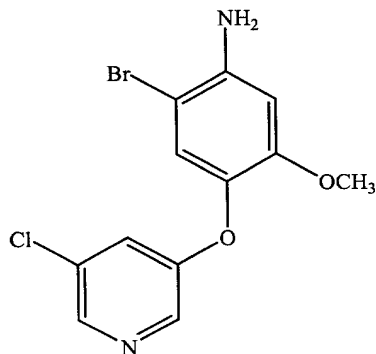
43.1

5-(4-(2,4-dichlorobenzenesulfonamido)-2-cyano-3-bromophenoxy)-3-chloropyridine was prepared in 28% yield from **42.1** and 2,4-dichlorobenzenesulfonyl chloride using the method of Example 3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.7 (s, 1H), 8.59 (d, *J* = 1.6 Hz, 1H), 8.53 (d, *J* = 2 Hz, 1H), 8.05 (bs, 1H), 7.9 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.6 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 9.2 Hz, 1H). MS (EI): *m/z* 537 (20, M+H), 535 (73, M+H), 533 (100, M+H), 531 (52, M+H).

EXAMPLE 44

10 This example illustrates the preparation of 5-(4-amino-5-bromo-2-methoxyphenoxy)-3-chloropyridine (**44.1**).



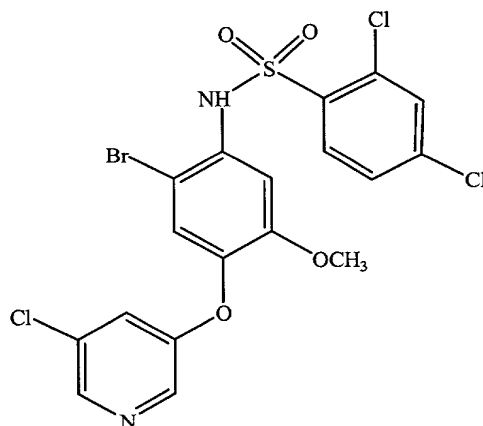
44.1

To a 0.2M solution of 5-(4-amino-2-methoxyphenoxy)-3-chloropyridine (200 mg, 0.8 mmol, **22.1**) in CH₂Cl₂ at 0 °C was added 2,4,4,6-tetrabromo-2,5-cyclohexadieneone (334 mg, 0.82 mmol, Lancaster). The resulting solution was stirred for 21 hours at ambient temperature. The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed twice with a 2M solution of aqueous sodium hydroxide (50 mL), once with brine (50 mL), dried over Na₂SO₄, and concentrated under vacuum. The crude solid was purified by column chromatography (0-2% MeOH in CH₂Cl₂) to furnish 133 mg (50%) of the title compound as a brown solid.

¹H NMR (400MHz, DMSO-*d*₆) δ 8.27 (d, *J* = 2.2 Hz, 1H), 8.17 (d, *J* = 2.6 Hz, 1H), 7.26 (dd, *J* = 2.3, 1.9 Hz, 1H), 7.24 (s, 1H), 6.64 (s, 1H), 5.38 (s, 2H), 3.65 (s, 3H). MS (EI): *m/z* 329 (80, M+H), 330 (12, M+H), 331 (100, M+H), 332 (16, M+H), 333 (28, M+H), 334 (4, M+H).

EXAMPLE 45

This example illustrates the preparation of 5-(4-(2,4-dichlorobenzene-sulfonainido)-5-bromo-2-methoxyphenoxy)-3-chloropyridine (**45.1**).



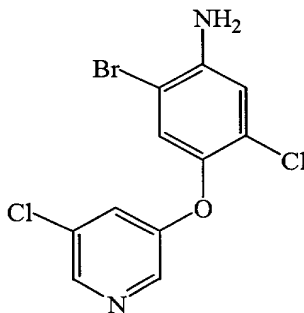
45.1

5-(4-(2,4-dichlorobenzene-sulfonamido)-5-bromo-2-methoxyphenoxy)-3-chloropyridine was prepared in 25% yield from **44.1** and 2,4-dichlorobenzene-sulfonyl chloride using the method of Example 3.

$^1\text{H NMR}$ (400MHz, $\text{DMSO}-d_6$) δ 10.4 (s, 1H), 8.36 (d, $J = 1.8$ Hz, 1H), 8.2 (d, $J = 2.5$ Hz, 1H), 7.9 (d, $J = 8.6$ Hz, 1H), 7.9-7.65 (m, 1H), 7.68 (bs, 1H), 7.59 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.45 (s, 1H), 7.42 (dd, $J = 2.4, 1.9$ Hz, 1H), 6.99 (s, 1H), 3.65 (s, 3H).
MS (EI): m/z 537 (58, M+H), 538 (10, M+H), 539 (100, M+H), 540 (20, M+H), 541 (70, M+H), 542 (15, M+H), 543 (25, M+H).

EXAMPLE 46

15 This example illustrates the preparation of 5-(4-amino-5-bromo-2-chlorophenoxy)-3-chloropyridine (**46.1**).



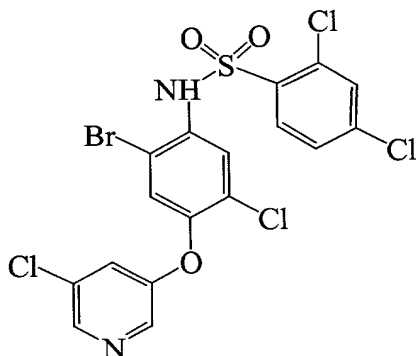
46.1

5-(4-Amino-5-bromo-2-chlorophenoxy)-3-chloropyridine was synthesized (43%) in a similar manner as described by Example 44 using 3-chloro-4-(3-chloro-5-pyridyloxy)aniline (**15.1**).

¹H NMR (400MHz, DMSO-*d*₆) δ 8.35 (d, J = 1.9 Hz, 1H), 8.23 (d, J = 2.5 Hz, 1H), 7.48 (s, 1H), 7.41 (dd, J = 2.4, 2.2 Hz, 1H), 6.98 (s, 1H), 5.62 (s, 2H). MS (EI): *m/z* 333 (55, M+H), 334 (12, M+H), 335 (90, M+H), 336 (12, M+H), 337 (40, M+H), 338 (5, M+H).

EXAMPLE 47

10 This example illustrates the preparation of 5-(4-(2,4-dichlorobenzenesulfonamido)-5-bromo-2-chlorophenoxy)-3-chloropyridine (**47.1**).



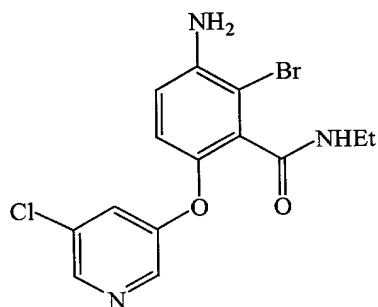
47.1

15 5-(4-(2,4-dichlorobenzenesulfonamido)-5-bromo-2-chlorophenoxy)-3-chloropyridine was prepared in 17% yield from **46.1** and 2,4-dichlorobenzenesulfonyl chloride using the method of Example 3.

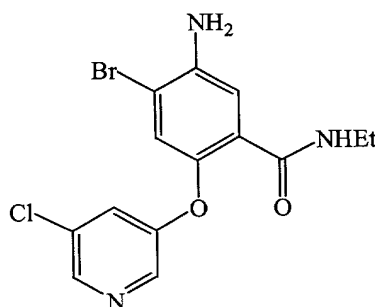
¹H NMR (400 MHz, DMSO-*d*₆) δ 10.6 (s, 1H), 8.47 (d, J = 2.2 Hz, 1H), 8.34 (d, J = 2.6 Hz, 1H), 7.89 (d, J = 2.1 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.7 (dd, J = 2.3, 2.2 Hz, 1H), 7.6 (dd, J = 8.5, 2.0 Hz, 1H), 7.55 (s, 1H), 7.47 (s, 1H). MS (EI): *m/z* 539 (40, M-H), 540 (10, M-H), 541 (100, M-H), 542 (20, M-H), 543 (80, M-H), 544 (25, 20 M-H), 545 (35, M-H), 546 (5, M-H).

EXAMPLE 48

25 This example illustrates the preparation of 5-(3-chloro-4-amino-2-(N-ethylcarboxamidophenoxy))-3-chloropyridine (**48.1**) and 5-(5-chloro-4-amino-2-(N-ethylcarboxamidophenoxy))-3-chloropyridine (**48.2**).



48.1



48.2

To a 0.1M solution of 5-(4-amino-2-(N-ethylcarboxamidophenoxy))-3-chloropyridine, (1 g, 3.6 mmol, prepared as described in Ser. No. 09/234,327) in AcOH was added bromine (194 μ L, 3.8 mmol) and the resulting solution was stirred for 2 days.

5 Most of the AcOH was azeotropically removed using hexanes and the resulting solution was adjusted to pH 6 using a 4M aqueous solution of NaOH. The aqueous layer was extracted three times with EtOAc (50 mL) and the combined organic layers were washed twice with an aqueous brine solution (100 mL), dried over Na₂SO₄, and concentrated under vacuum. The crude solid was purified by chromatography (50-100% EtOAc in

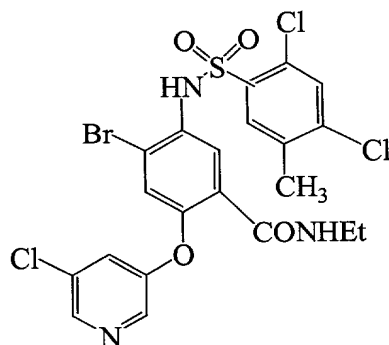
10 hexanes) to separate the products **48.1** and **48.2** from the starting materials and dibrominated materials. The desired products were then rechromatographed (1-3% MeOH in CH₂Cl₂) to furnish 478 mg (36%) of **48.1** and 198 mg (15%) of **48.2** as white solids.

48.1: ¹H NMR (400MHz, DMF50-*d*₆) δ 8.37 (t, J = 5.2 Hz, 1H), 8.3 (bs, 1H), 8.24 (d, J = 2.2 Hz, 1H), 7.38 (m, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 3.1 (pentet, J = 7.0 Hz, 2H), 0.91 (t, J = 7.1 Hz, 3H). MS (EI): *m/z* 370 (80, M+H), 371 (15, M+H), 372 (100, M+H), 373 (18, M+H), 374 (25, M+H).

48.2: ¹H NMR (400MHz, DMSO-*d*₆) δ 8.3 (d, J = 1.75 Hz, 1H), 8.23 (t, J = 5.4 Hz, 1H), 8.2 (d, J = 2.0 Hz, 1H), 7.34-7.28 (m, 2H), 6.99 (d, J = 1.6 Hz, 1H), 3.08 (pentet, J = 7.2 Hz, 2H), 0.88 (t, J = 7.3 Hz, 3H). MS (EI): *m/z* 370 (80, M+H), 371 (15, M+H), 372 (100, M+H), 373 (18, M+H), 374 (25, M+H).

EXAMPLE 49

This example illustrates the preparation of 5-(5-bromo-4-(2,4-dichloro-5-methylbenzenesulfonamido)-2-(N-ethylcarboxamido)phenoxy)-3-chloropyridine (**49.1**).



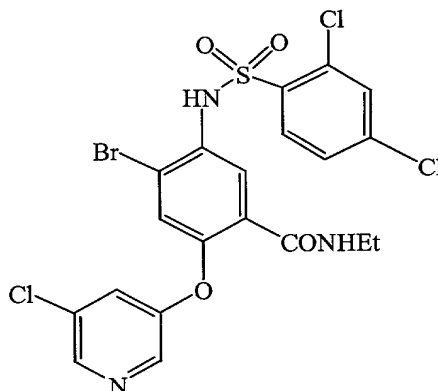
49.1

The title compound was prepared in 67% yield from **48.1** and 2,4-dichloro-5-ethylbenzenesulfonyl chloride using the method of Example 3.

¹H NMR (400MHz, DMSO-*d*₆) δ 10.41 (s, 1H), 8.48 (d, J = 2.1 Hz, 1H), 8.35 (t, J = 5.4 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 7.85 (bs, 2H), 7.6 (dd, J = 2.3, 2.2 Hz, 1H), 7.41 (s, 1H), 7.39 (s, 1H), 3.14 (pentet, J = 7.2 Hz, 2H), 2.34 (s, 3H), 0.94 (t, J = 7.2 Hz, 3H). MS (EI): *m/z* 597 (8, M-H), 596 (25, M-H), 595 (20, M-H), 594 (70, M-H), 593 (30, M-H), 592 (100, M-H), 591 (12, M-H), 590 (50, M-H).

EXAMPLE 50

This example illustrates the preparation of 5-(5-bromo-4-(2,4-dichlorobenzenesulfonylamido)-2-(N-ethylcarboxamido)phenoxy)-3-chloropyridine (**50.1**).



50.1

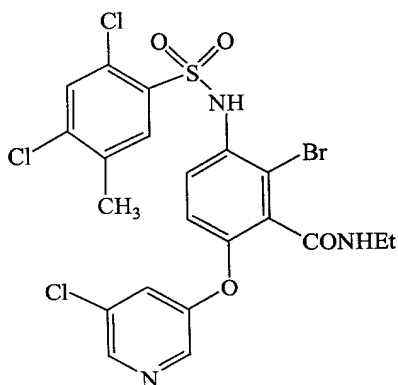
The title compound was prepared in 28% yield from **48.1** and 2,4-dichloro-benzenesulfonyl chloride using the method of Example 3.

¹H NMR (400MHz, DMSO-*d*₆) δ 10.5 (s, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.34 (t, J = 5.6 Hz, 1H), 8.31 (d, J = 2.3 Hz, 1H), 7.9 (d, J = 2.0 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.62 (dd, J = 2.4, 2.1 Hz, 1H), 7.59 (dd, J = 8.6, 2.2 Hz, 1H), 7.41 (s, 1H), 7.38

(s,1H), 3.14 (pentet, J = 7.0 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). MS (EI): m/z 585 (8, M+H), 584 (25, M+H), 583 (18, M+H), 582 (70, M+H), 581 (25, M+H), 580 (100, M-H), 579 (12, M+H), 578 (50, M+H).

EXAMPLE 51

- 5 This example illustrates the preparation of 5-(3-bromo-4-(2,4-dichloro-5-methylbenzenesulfonamido)phenoxy)-3-chloropyridine (**51.1**).



51.1

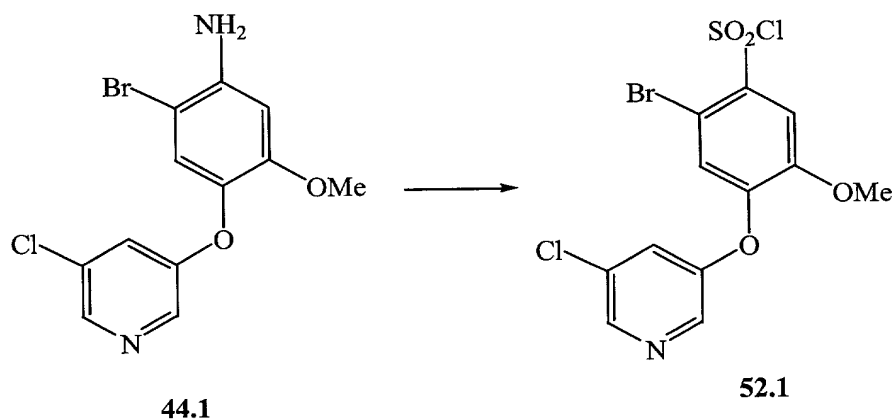
The title compound was prepared in 37% yield from **48.2** and 2,4-dichloro-5-methylbenzenesulfonyl chloride using the method of Example 3.

- 10 ^1H NMR (400MHz, DMSO- d_6) δ 10.39 (s, 1H), 8.55 (t, 1H), 8.42 (d, 1H), 8.31 (d, 1H), 7.89 (s, 1H), 7.88 (s, 1H), 7.6 (dd, 1H), 7.12 (d, 1H), 7.02 (d, 1H), 3.14 (pentet, 2H), 2.35 (s, 3H), 0.94 (t, 3H). MS (EI): m/z 599 (8, M+H), 598 (25, M+H), 597 (18, M+H), 596 (70, M+H), 595 (25, M+H), 594 (100, M-H), 593 (12, M+H), 592 (50, M+H).

15

EXAMPLE 52

This example illustrates the synthesis of 5-(5-bromo-4-chlorosulfonyl-2-methoxyphenoxy)-3-chloropyridine (**52.1**).

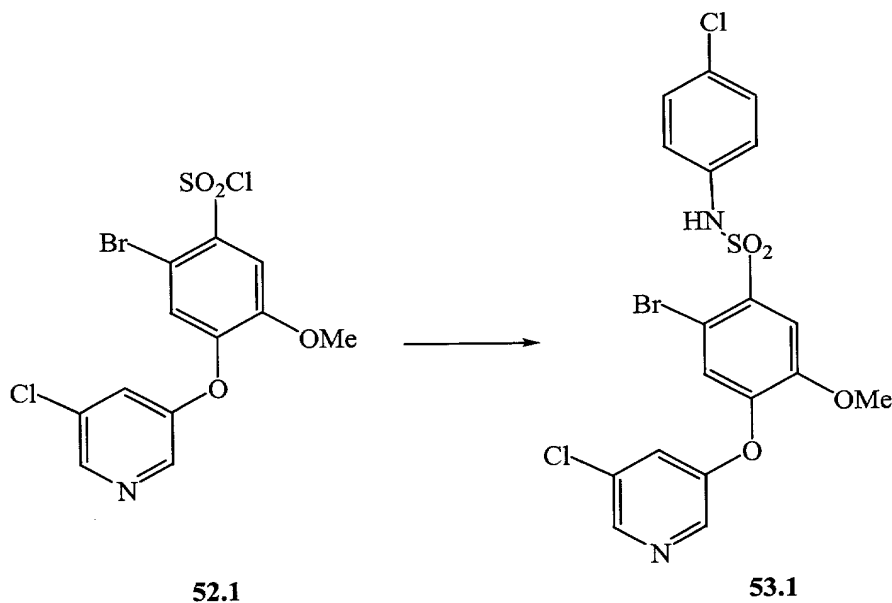


Compound **44.1** (1.20 g, 3.66 mmol) was converted to the title compound using the general procedure of R. V. Hoffman (Org. Syn. Coll. Vol., VII, 508-511), to provide 1.26 g (84%) of **52.1** as a clear oil which was carried on without purification.

MS ESI m/e: 412.0(M+H).

EXAMPLE 53

This example illustrates the preparation of **53.1**.

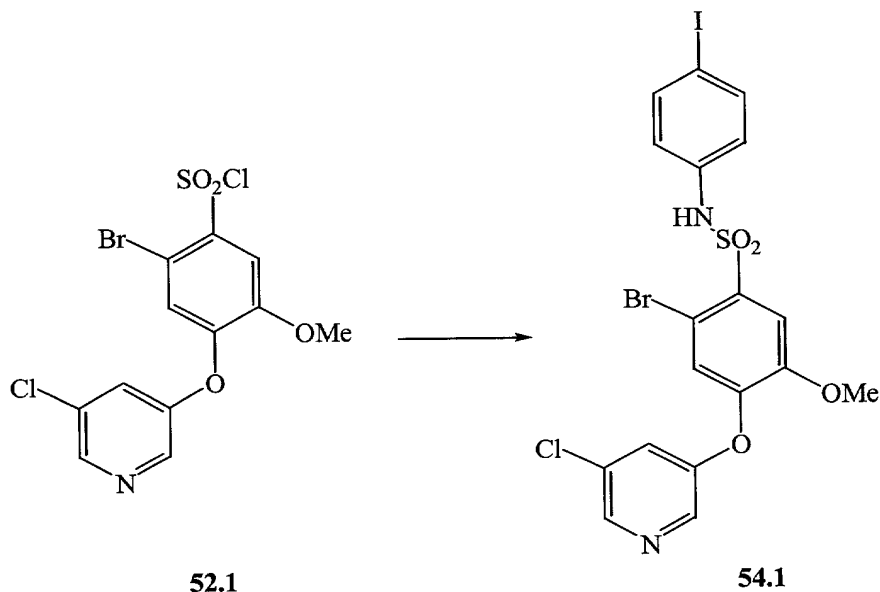


4-Chloroaniline (73 mg, 0.57 mmol, Aldrich Chemical Co.), 5-(5-bromo-4-chlorosulfonyl-2-methoxyphenoxy)-3-chloropyridine (236 mg, 0.57 mmol), pyridine (45 mg, 0.57 mmol), catalytic DMAP, and 2 mL of methylene chloride were combined using the general method of Example 35. The title compound was obtained (245 mg, 85%) as a white solid.

^1H NMR (400MHz) (d_6 -DMSO) δ 10.80 (1H, s); 8.43 (1H, d, $J=2.0$ Hz); 8.30 (1H, d, $J=2.4$ Hz); 7.74 (1H, s); 7.64 (1H, dd, $J=4.4$ Hz, 2.2 Hz); 7.52 (1H, s); 7.31 (2H, dd, $J=8.8$ Hz, 2.1 Hz); 7.14 (1H, dd, $J=8.8$ Hz, 2.1 Hz); 3.83 (3H, s). MS ESI m/e : 435.0 (M - H).

EXAMPLE 54

This example illustrates the preparation of **54.1**.

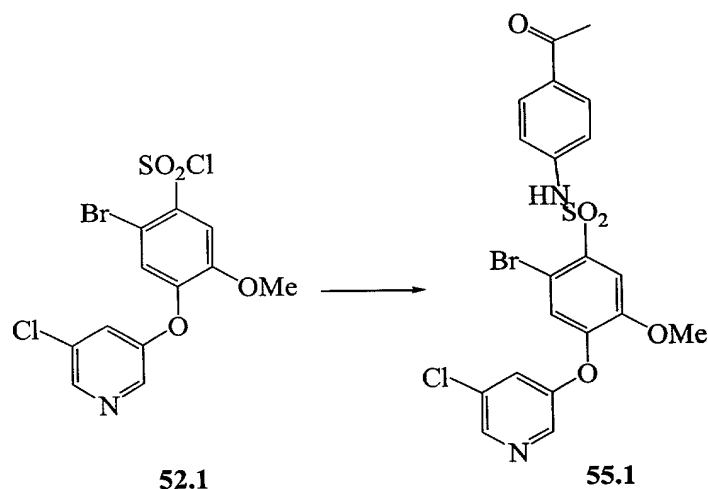


In a manner similar to that described in Example 53, 4-iodoaniline (83 mg, 0.38 mmol), 5-(5-bromo-4-chlorosulfonyl-2-methoxyphenoxy)-3-chloropyridine (155 mg, 0.38 mmol), pyridine (30 mg, 0.38 mmol), catalytic DMAP, and 2 mL of methylene chloride were combined and stirred. After workup, the title compound was obtained (162 mg, 73%) as a white solid.

^1H NMR (400MHz) (d_6 -DMSO) δ 10.80 (1H, s); 8.43 (1H, d, $J=2.0$ Hz); 8.31 (1H, d, $J=2.4$ Hz); 7.75 (1H, s); 7.64 (1H, dd, $J=4.4$ Hz, 2.2 Hz); 7.58 (2H, m); 7.51 (1H, s); 6.95 (1H, dd, $J=8.6$ Hz, 2.2 Hz); 3.84 (3H, s). MS ESI m/e : 592.8 (M - H).

EXAMPLE 55

This example illustrates the preparation of **55.1**.

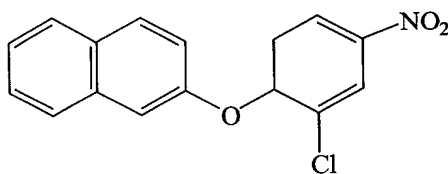


In a manner similar to that described in Example 53, 4-acetylaniline (69 mg, 0.51 mmol), 5-(5-bromo-4-chlorosulfonyl-2-methoxyphenoxy)-3-chloropyridine (210 mg, 0.51 mmol), pyridine (40 mg, 0.51 mmol), catalytic DMAP, and 2 mL of methylene chloride were combined and stirred. After workup, the title compound was obtained (192 mg, 74%) as a white solid.

^1H NMR (400MHz) (d_6 -DMSO) δ 10.80 (1H, s); 8.43 (1H, d, $J=2.0$ Hz); 8.31 (1H, d, $J=2.4$ Hz); 7.75 (1H, s); 7.64 (1H, dd, $J=4.4$ Hz, 2.2 Hz); 7.58 (2H, m); 7.51 (1H, s) 6.95 (1H, dd, $J=8.6$ Hz, 2.2 Hz); 3.84 (3H, s). MS ESI in/e: 509.0 (M - H).

EXAMPLE 56

This example illustrates the preparation of 3-chloro-4-(2-naphthylxoy)nitrobenzene (56.1).



56.1

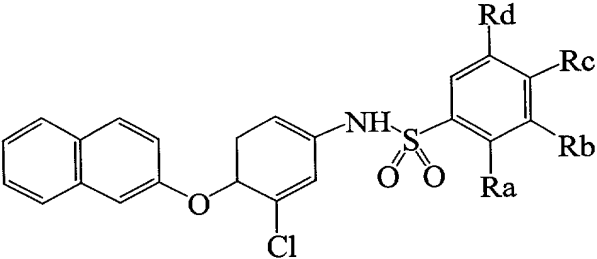
To a 250 mL flask, were added 3-chloro-4-fluoro-nitrobenzene (Aldrich)(5.0 g, 28 mmol), 2-naphtol (Aldrich)(4.5g, 31 mmol), Cs_2CO_3 (Aldrich)(9.7g, 30 mmol) and DME (80 mL). The mixture was heated at 100 °C overnight. After removal of DMF under vacuum, the mixture was poured into water and extracted with dichloromethane. The organic solution was then washed with brine, dried over magnesium sulfate. After filtration, the filtrate was concentrated under vacuum to give a crude product, which was then chromatographed with eluent (30% dichloromethane / hexanes) to give the title compound (6.8 g, 24 mmol, 86%).

EXAMPLE 57

This example illustrates the preparation of compounds **57.1**, **57.2**, **57.3** and **57.4**.

- Compound **56.1** was reduced to the corresponding aniline derivative (**57.1**) using the procedure of Example 2, and converted to the compounds in Table 8 using commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

Table 8

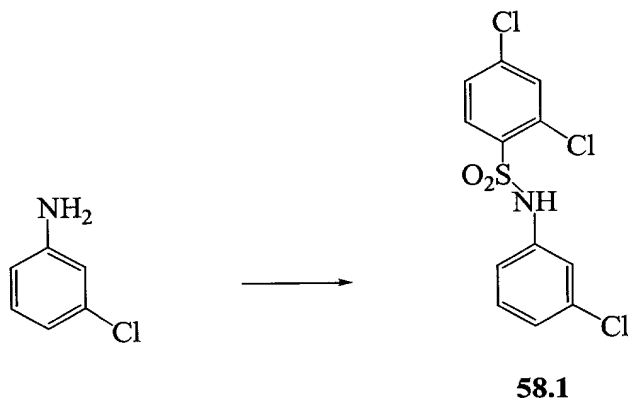


	Ra	Rb	Rc	Rd	m/e
57.2	Cl	H	Cl	H	476
57.3	Cl	H	I	H	534
57.4	H	H	OCH ₃	H	438

10

EXAMPLE 58

This illustrates the synthesis of 3-chloro-(2,4-dichlorobenzene-sulfonainido)benzene (**58.1**).



- The title compound was prepared using the method described in Example 3, starting with 800 mg (6.29 mmol) of 3-chloroaniline, 1.53 g (6.29 mmol) of 2,4-

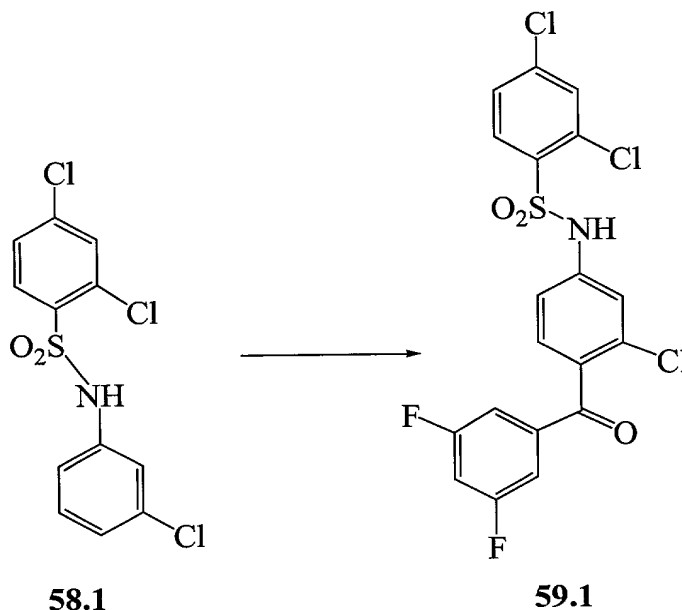
dichlorosulfonylchloride, 497 mg (6.29 mmol) of pyridine, catalytic DMAP, and 10 mL of methylene chloride. The title compound was obtained as a white foam (928 mg, 44%).

MS ESI m/e: 334.0 (M - H).

EXAMPLE 59

5

This example illustrates the synthesis of compound **59.1**.

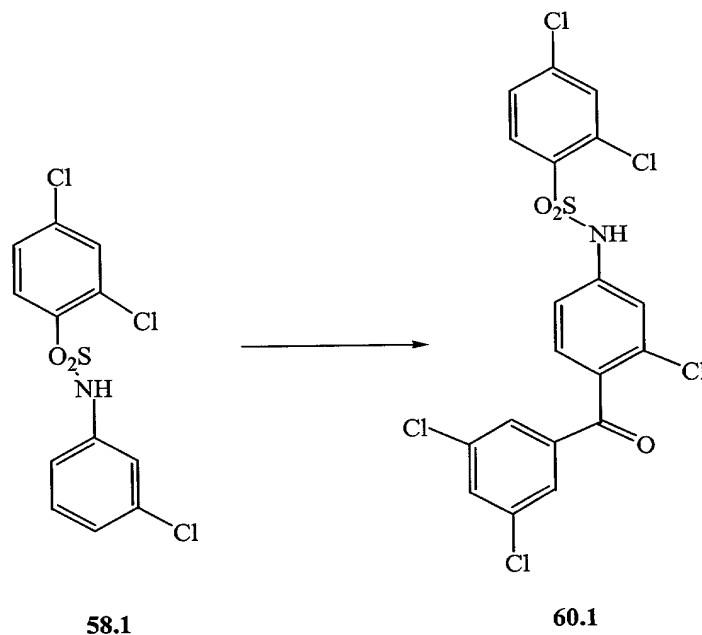


A round-bottomed flask was charged with 330 mg (0.99 mmol) of 3-chloro-(2,4-dichlorobenzenesulfonamido)benzene (**58.1**), 397 mg (2.97 mmol, Aldrich Chemical Co.) of anhydrous aluminum trichloride, and 2 mL of dry dichloroethane. Then 210 mg (1.19 mmol, Aldrich Chemical Co.) of 3,5-difluorobenzoyl chloride was added dropwise and the deep red solution was allowed to stir at room temperature overnight. The reaction was then diluted with 30 mL of methylene chloride, washed consecutively with 2N HCl and brine, dried over MgSO₄, and concentrated to a dark oil. This was further purified by silica gel flash chromatography (eluting with 1:24 ethyl acetate:methylene chloride). The resulting clear glaze was recrystallized from ether/hexanes to yield 273 mg (58%) of a white solid.

¹H NMR (400MHz) (d₆-DMSO) δ 8.15 (1H, d, J=8.5 Hz); 7.91 (1H, d, J=2.1 Hz); 7.68 (1H, dd, J=8.6 Hz, 2.1 Hz); 7.63 (1H, t, J=8.6 Hz); 7.46 (1H, d, J=8.4 Hz); 7.31 (2H, dd, J=7.8 Hz, 2.1 Hz); 7.23 (1H, d, J=1.9 Hz); 7.17 (1H, dd, J=8.4 Hz, 2.2 Hz). MS ESI m/e: 473.9 (M - H).

EXAMPLE 60

This illustrates the synthesis of compound 60.1.

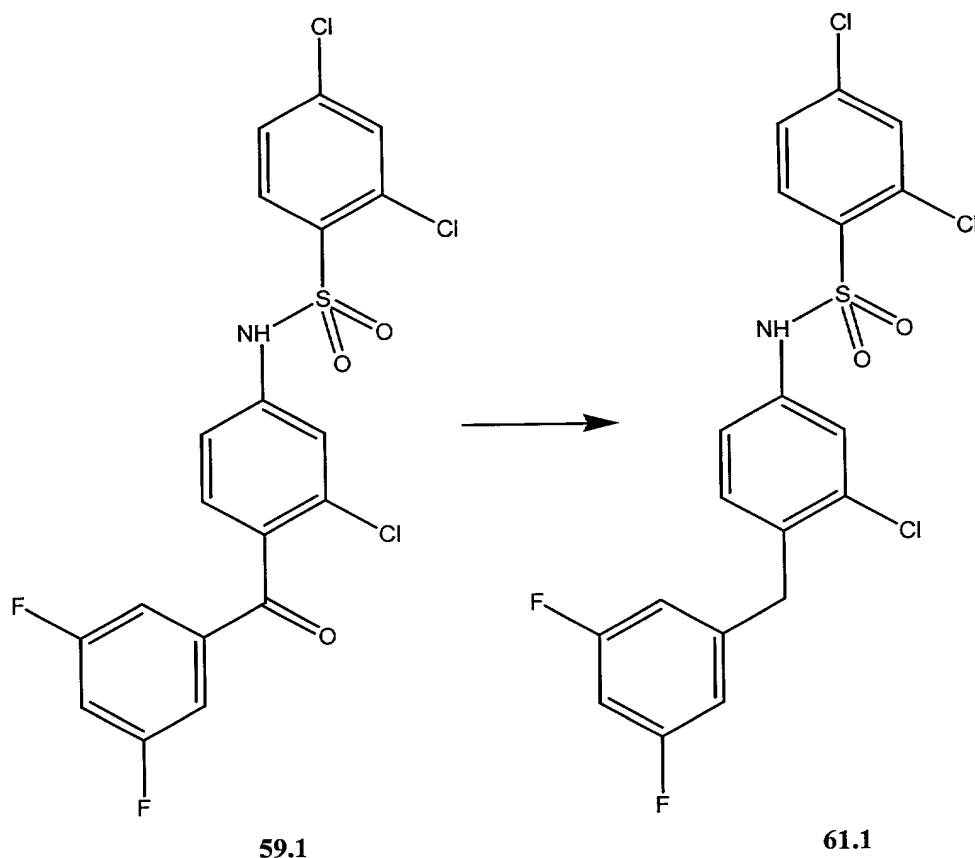


The title compound was prepared using the method of Example 59, starting with 286 mg (0.85 mmol) of 3-chloro-(2,4-dichlorobenzenesulfonamido)benzene (58.1), 341 mg (1.02 mmol) of anhydrous aluminum trichloride, 214 mg (1.02 mmol, Aldrich Chemical Co.) of 3,5-dichlorobenzoyl chloride, and 2 mL of dry dichloroethane. The title compound was obtained as a white solid (139 mg, 32%).

¹H NMR (400MHz) (*d*₆-DMSO) δ 11.49 (1H, s) 8.15 (1H, d, *J*=8.6 Hz); 7.97 (1H, d, *J*=3.8 Hz); 7.91 (1H, d, *J*=2.1 Hz); 7.69 (1H, dd, *J*=8.5 Hz, 2.0 Hz); 7.58 (2H, d, *J*=1.9 Hz); 7.47 (1H, d, *J*=8.4 Hz); 7.24 (1H, d, *J*=2.0 Hz); 7.17 (1H, dd, *J*=8.4 Hz, 2.1 Hz). MS ESI *m/e*: 505.9 (M - H).

EXAMPLE 61

This illustrates the synthesis of compound 61.1.

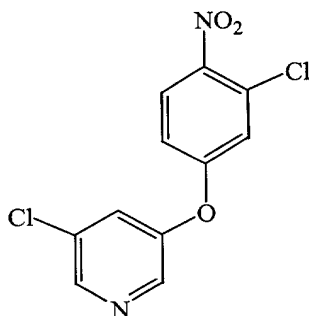


Biaryl ketone **59.1** (103 mg, 0.22 mmol) was reduced to the methylene compound **61.1** according to the procedure of West, *et. al.*, *J. Org. Chem.*, 38(15):2675-2681 (1973). The title compound was obtained as a white solid (86 mg, 86%).

¹H NMR (400MHz) (*d*₆-DMSO) δ 10.96 (1H, s) 8.05 (1H, d, *J*=8.6 Hz); 7.87 (1H, d, *J*=2.0 Hz); 7.63 (1H, dd, *J*=8.5 Hz, 2.1 Hz); 7.23 (1H, d, *J*=8.5 Hz); 7.14 (1H, d, *J*=2.2 Hz); 7.02 (2H, m); 7.17 (2H, m). MS ESI *m/e*: 460.0 (*M* - H).

EXAMPLE 62

This example illustrates the preparation of 2-chloro-4-(3-chloro-5-pyridyloxy)-nitrobenzene **62.1**.



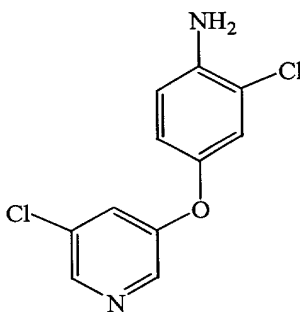
62.1

5 5-Chloro-3-pyridinol (5 g, Aldrich) and 2,4-dichloronitrobenzene (7.4 g, Aldrich) were combined as described in Example 1. The title compound was isolated as the minor product using gravity chromatography on silica eluting with 10% ethyl acetate / hexanes.

^1H NMR (400 MHz) (DMSO- d_6) δ 8.53 (s, 1H); 8.4 (s, 1H); 8.0 (d, $J=8.9$ Hz, 1H); 7.44 (t, $J=1.9$ Hz, 1H); 7.26 (d, $J=1.5$ Hz, 1H); 7.14 (d, $J=2.7$ Hz, 1H); 6.99 (dd, $J=9.0, 2.6$ Hz, 1H) 1.6 (impurity).

EXAMPLE 63

10 This example illustrates the preparation of 2-chloro-4-(3-chloro-5-pyridyloxy)-aniline 63.1.



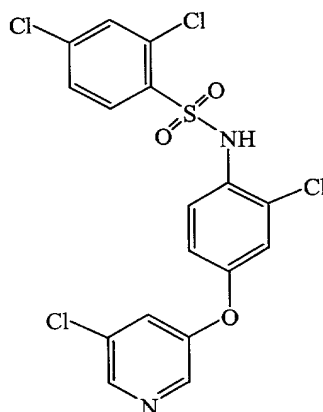
63.1

15 Compound 62.1 was reduced using the method of Example 2 to provide the title compound as a yellow solid.

^1H NMR (400 MHz) (DMSO) δ 8.33 (d, $J=2.1$ Hz, 1H); 8.25 (d, $J=2.4$ Hz, 1H); 7.41 (t, $J=2.2$ Hz, 1H); 7.12 (d, $J=2.6$ Hz, 1H); 6.91 (dd, $J=2.6, 8.8$ Hz, 1H); 6.84 (d, $J=8.8$ Hz, 1H); 5.35 (s, 2H).

EXAMPLE 64

This example illustrates the preparation of **64.1**.

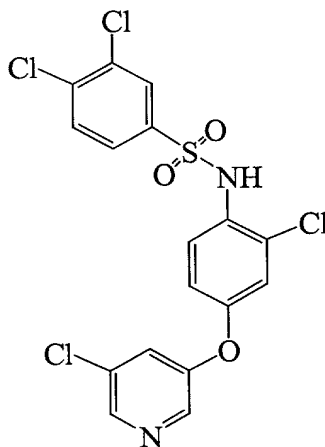


64.1

Compound **63.1** and 2,4-dichlorobenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The crude product was purified by flash chromatography on silica eluting with dichloromethane. The resulting product was then triturated in diethyl ether/hexanes to furnish the title compound as a white solid. MS ESI m/e: 461 (M-H).

EXAMPLE 65

This example illustrates the preparation of **65.1**.



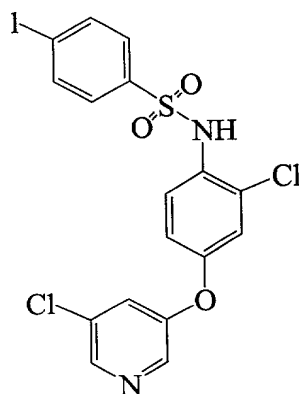
65.1

Compound **63.1** and 3,4-dichlorobenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The crude product was purified by flash chromatography on silica eluting with 5% ethyl acetate/

dichloromethane. The resulting product was then triturated in hexanes to furnish the title compound as a white solid. MS ESI m/e: 461 (M-H).

EXAMPLE 66

This example illustrates the preparation of 66.1.



66.1

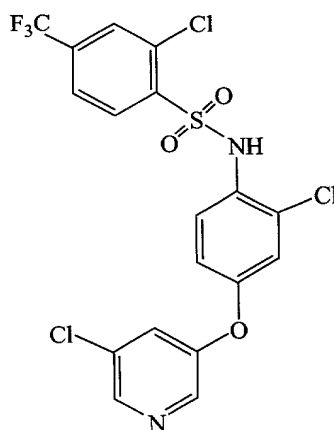
5

Compound 63.1 and 4-iodobenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The crude product was purified by flash chromatography on silica eluting with dichloromethane. The resulting product was then triturated in hexanes to furnish the title compound as a white solid. MS

10 ESI m/e: 519 (M-H).

EXAMPLE 67

This example illustrates the preparation of 67.1.



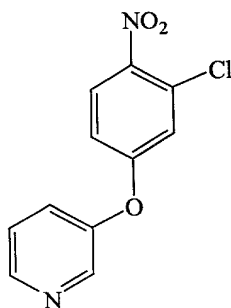
67.1

15 Compound 63.1 and 2-chloro-4-trifluoromethylbenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The

crude product was purified by flash chromatography on silica eluting with 5% ethyl acetate / dichloromethane. The resulting product was then triturated in hexanes to furnish the title compound as a white solid. MS ESI m/e: 495 (M-H).

EXAMPLE 68

- 5 This example illustrates the preparation of 2-chloro-4-(3-pyridyloxy)nitrobenzene (**68.1**).



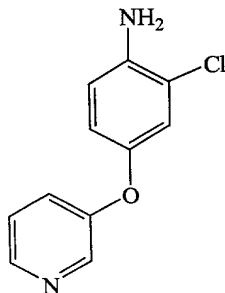
68.1

- 2,4-Dichloronitrobenzene (10.2 g, Aldrich) and 3-hydroxypyridine (5 g, Aldrich) were combined using the method of Example 1, to provide the 0.82 g of the title
10 compound as a yellow solid.

^1H NMR (400 MHz) (CDCl_3) δ 8.58 (s, 1H); 8.52 (s, 1H); 8.0 (d, $J=9.0$ Hz, 1H); 7.44 (s, 2H); 7.10 (d, $J=2.6$ Hz, 1 H) 6.96 (dd, $J=9.0, 6.65$ Hz).

EXAMPLE 69

- This example illustrates the preparation of 2-chloro-4-(3-pyridyloxy)aniline.
15

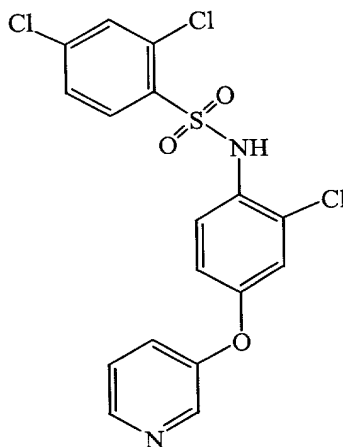


Compound **68.1** was reduced using the method of Example 2 to provide the title compound as a brown oil, which was used without further purification.

- ^1H NMR (400 MHz) (DMSO) δ 8.29-8.26 (m, 2H); 7.35 (dd, $J=4.6, 8.4$ Hz, 1H); 7.29-7.26 (m, 1H); 7.04 (d, $J=2.0$ Hz, 1H); 6.85-6.84 (m, 2H); 5.29 (s, 2H).
20

EXAMPLE 70

This example illustrates the preparation of 70.1.

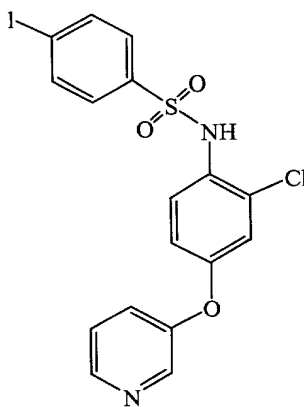


70.1

Compound 69.1 and 2,4-dichlorobenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The crude product was purified by flash chromatography on silica eluting with 5% ethyl acetate/dichloromethane. The resulting product was then triturated in diethyl ether to furnish the title compound as a white solid. MS ESI m/e: 429 (M-H).

EXAMPLE 71

This example illustrates the preparation of 71.1.



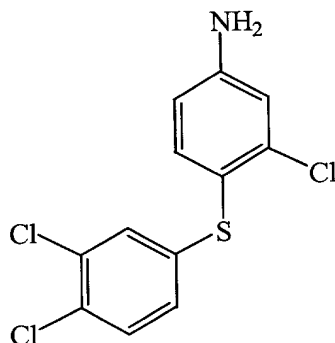
71.1

Compound 69.1 and 4-iodobenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The crude product was purified using flash chromatography on silica eluting with 5-20% ethyl acetate/

dichloromethane. The resulting product was then triturated in diethyl ether to furnish the title compound as a white solid. MS ESI m/e: 485 (M-H).

EXAMPLE 72

This example illustrates the preparation of **72.1**.



72.1

5

To a solution of 3,4-dichlorothiophenol (0.87 mL) and 4-fluoro-3-chloronitrobenzene (1.2 g) in THF (12 mL) was added a solution of potassium *t*-butoxide in THF (1 M, 3.7 mL). Ethanol was added to form a precipitate and the mixture was heated to dissolve the solid. The mixture was then cooled to ambient temperature and water was added. The resulting solids were collected by filtration and washed with water. The product was dissolved in methylene chloride, dried over magnesium sulfate, filtered and concentrated to provide a yellow nitro intermediate (2.08 g).

10

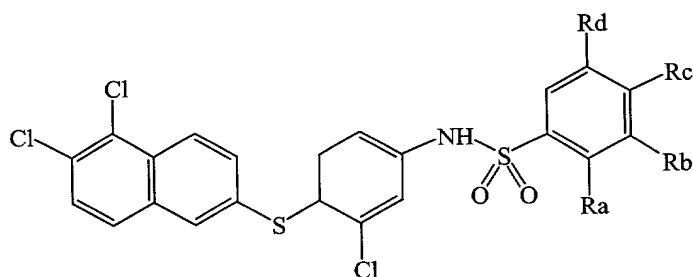
SnCl_2 hexahydrate (7 g) was added to a solution of the intermediate nitro compound in ethyl acetate (40 mL) at 85°C. After 12 hr, the reaction was treated with 420 mL of 0.5 N NaOH solution and diluted with EtOAc (100 mL). The milky suspension was filtered through Celite and rinsed with additional EtOAc. The layers were separated and the water layer was extracted with additional EtOAc. The combined organic portions were dried over MgSO_4 , filtered and concentrated under vacuum to provide the aniline derivative **72.1**, which was used without purification.

15

The compounds provided in Table 9 were prepared using **72.1** and commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

20

Table 9

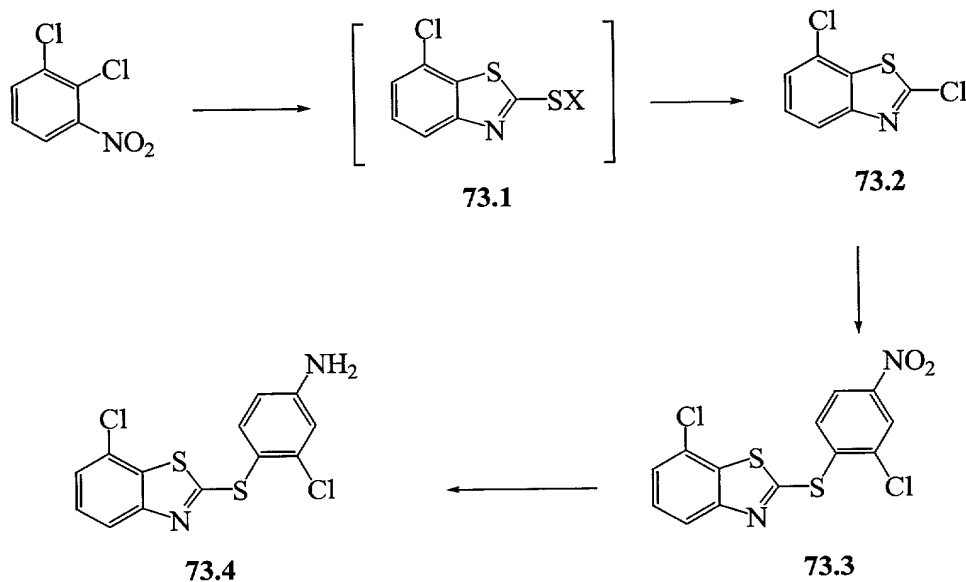


	Ra	Rb	Rc	Rd	m/e (M-H)
72.2	H	Cl	Cl	H	510
72.3	Cl	H	Cl	H	510
72.4	H	H	I	H	568

Compound **72.3** was converted to the corresponding biaryl sulfoxide (**72.5**, m/e 526) and biaryl sulfone (**72.6**, m/e 542) using an oxone procedure (see, for example, Trost, *et al.*, *Tetrahedron Lett.*, **22**:1287 (1981) and Webb, *Tetrahedron Lett.*, **35**:3457-3460 (1994)). Similarly, compound **72.2** was converted to the biaryl sulfoxide (**72.7**, m/e 526) using a routine oxidation with mCPBA.

EXAMPLE 73

This example illustrates the preparation of **73.4** through **73.9**.



2,3 dichloronitrobenzene (19.04g) was suspended in 40% Na_2CS_3 solution in water (66 ml) with 5 ml of ethanol and heated at 130°C bath temperature for 3 days. After cooling, the residue was diluted in water and acidified with 5N HCl (caution:

foaming gas evolution). The tan solids were collected by filtration, rinsed with water and dried under vacuum to give 19.9g of an intermediate complex (**73.1**). The crude **73.1** (6.03 g) was added to neat sulfonyl chloride (20 ml) cautiously over about 5 minutes. The mixture was then heated at 50° C. The character of the solid changed but did not dissolve. The reaction was quenched by pouring onto ice. The ice mixture was stirred until the initial heavy dark oil solidified. The solids were collected by filtration, dissolved in ethyl ether and washed with water. The product was purified by flash chromatography using hexane, then 20% methylene chloride/hexane to afford 3.2 g of a 2,7-dichlorobenzothiazole (**73.2**) as a low melting solid.

¹H NMR (CDCl₃) δ 7.823 (d, J=8.4 Hz), 7.417 (t, J=8.4 Hz), 7.371 (d, J=8.4 Hz). Anal. calc: 41.20% C, 1.48% H, 6.86 % N; found: 41.06 %C, 1.46% H, 6.75% N

3-Chloro-4-mercapto nitrobenzene (prepared by the method of Price and Stacy, *J. Amer. Chem. Soc.* 68, 498-500 (1946)) (1.33 g) and 2,7-dichlorobenzothiazole (**73.2**) (1.43g) were dissolved in ethanol (20 ml) with heating. Pyridine (1.1g, 2 eq) was added. After a solid formed, additional ethanol (20 ml) was added and the mixture maintained at 50° C overnight. The solid was collected by filtration and rinsed with water. The solids were dried as a solution in methylene chloride and concentrated to afford the nitro compound **73.3** (2.22g) as an off-white solid. (mp 210-212°C)

¹H NMR (DMSO) δ 8.544 (d, J=2.4 Hz, 1H), 8.273 (dd, J=8.8, 2.5 Hz, 1H), 8.081 (d, J=8.6 Hz, 1H), 7.961 (dd, J=6.3, 2.4 Hz, 1H), 7.60 (m, 2H).

Using the method of example 32, the nitro derivative **73.3** was converted to the corresponding aniline (**73.4**). Flash chromatography gave a white solid. (mp 165-167°C).

¹H NMR (DMSO) δ 7.775 (d, J=8.4 Hz, 1H), 7.606 (d, J=8.0 Hz, 1H), 7.367 (t, J=8.0 Hz, 1H), 7.265 (d, J=8.0 Hz, 1H), 6.931 (d, J=2.0 Hz, 1H), 6.672 (dd, J=8.4, 2.4 Hz, 1H), 4.15 (br s, 2H). ESI MS 327 (M+H). Anal. calcd. 47.71% C, 2.46% H, 8.56 % N; found: 47.93 %C, 2.48 % H, 8.47% N

Reaction of 2-chloro-4-trifluoromethylbenzene sulfonyl chloride with aniline **73.4** according to the method of Example 3 gave sulfonamide **73.5** (see Table 10).

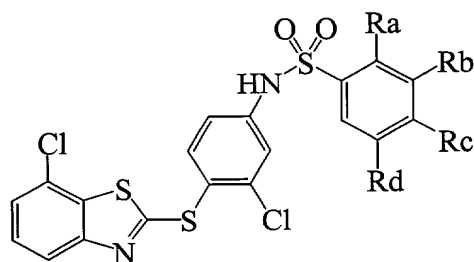
¹H NMR (DMSO) δ 11.712 (br s, 1H), 8.377 (d, J=8.4 Hz, 1H), 8.187 (d, J=2 Hz, 1H), 7.995 (dd, J=8.4, 1.2 Hz, 1H), 7.880 (d, J=8.4 Hz, 1H), 7.822 (dd, 7.2, 2.0 Hz, 1H), 7.509 (t, J=8.0 Hz, 1H), 7.474 (dd, J=7.6, 2.0 Hz, 1H), 7.443 (d, J=2.4 Hz, 1H),

7.256 (dd, $J=8.8, 2.4$ Hz, 1H). MS (M+H) 569; MS (M-H) 567. Anal. calcd. 42.15% C, 1.77% H, 4.92 % N; found: 42.30 %C, 1.76 % H, 4.94% N.

The additional compounds provide in Table 10 were prepared similarly using aniline **73.4** and the corresponding sulfonyl chlorides using the method of Example

5 3.

Table 10



		Ra	Rb	Rc	Rd	m/e (M-H)
10	73.5	Cl	H	CF ₃	H	567
	73.6	H	Cl	Cl	H	533
	73.7	Cl	H	Cl	H	533
	73.8	H	H	I	H	591
	73.9	Cl	H	Cl	Me	547

15

EXAMPLE 74

The following benzenesulfonyl chlorides were prepared by the procedure of R. V. Hoffman (Org. Syn. Coll. Vol. VII, 508-511) from the corresponding commercially available anilines and used to make the indicated examples.

20

74a 2-chloro-4-t-butylbenzenesulfonyl chloride. yield 34%
for examples 76.8 and 79.9

¹H NMR (CDCl₃) δ 8.06 (1H, d, $J = 8.4$ Hz), 7.62 (1H, s), 7.48 (1H, d, $J = 8.4$ Hz), 1.37 (9H, s)

m.p. 68.8 °C

25

74b 2-trifluoromethyl-4-chlorobenzenesulfonyl chloride. yield 76% as a solid.

for examples 176 and 347

¹H NMR (CDCl₃) δ 8.325 (d, $J=8.4$ Hz, 1H), 7.966 (br s, 1H), 7.829 (br d, $J=8.4$ Hz, 1H)

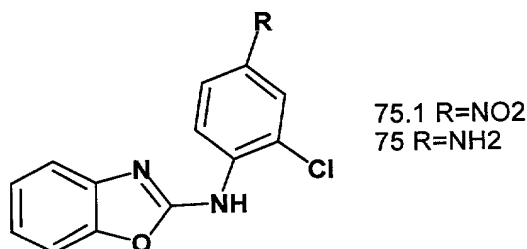
m.p. 37.0 °C

74c 2-chloro-4-methylbenzenesulfonyl chloride. yield 47% as an oil.
for examples 76.9, 79.8 and 351.

¹H NMR (CDCl₃) δ 8.02 (1H, d, *J* = 8.8 Hz), 7.46 (1H, s), 7.28 (1H, d, *J* =
5 8.8 Hz), 2.47 (3H, s)

EXAMPLE 75

This illustrates the synthesis of compound **75**.



10 By the method of example 201, 2-chlorobenzoxazole (5 g) and 2-chloro-4-nitroaniline (6.1 g) were coupled to provide nitro compound **75.1** (2.6g) as a yellow solid.

¹H NMR (d₆-acetone) δ 9.514 (s, 1H), 9.01 (d, *J*=9 Hz, 1H), 8.4 (s, 1H), 8.37 (dd, *J*=8.4, 2 Hz, 1H), 7.58 (d, *J*=8.4 Hz, 1H), 7.52 (d, *J*=8 Hz, 1H), 7.34 (t, *J*=7.6 Hz, 1H), 7.28 (t, *J*= 7.6 Hz, 1H). MS (M-H) 288; (2M-2H+Na) 599

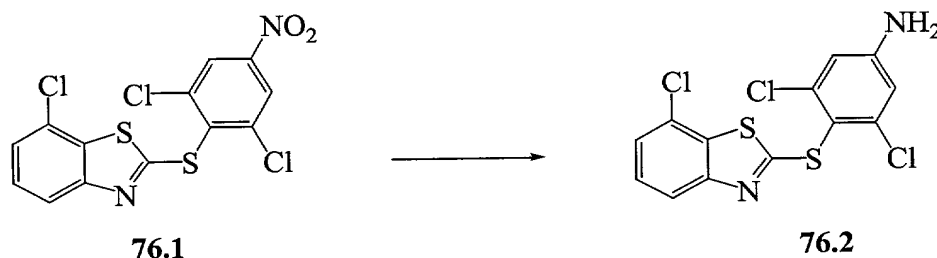
15 Reduction by the method of example 32 gave the aniline **75** (93%) as a grey solid.

¹H NMR (d₆-acetone) δ 8.45 (br s, 1H), 7.796 (d, *J*=8.4 Hz, 1H), 7.353 (d, *J*=7.6 Hz, 1H), 7.335 (d, *J*=7.6 Hz, 1H), 7.191 (t, *J*=7.6 Hz, 1H), 7.088 (t, *J*=8 Hz, 1H), 6.846 (d, *J*=2.4 Hz, 1H), 6.673 (dd, *J*=8.8, 2.4 Hz, 1H), 4.912 (br s, 2H). MS (M+H)

20 260.1

EXAMPLE 76

This example illustrates the preparation of **76.2** and sulfonamides derived from it.



25

3,5-dichloro-4-mercapto nitrobenzene (prepared by the method of Price and Stacy, *J. Amer. Chem. Soc.* 68, 498-500 (1946)) (0.65g) and 2,7-dichlorobenzothiazole (**73.2**) were combined by the method of Example 73, to afford the nitro derivative (**76.1**) as a yellow solid (0.95g).

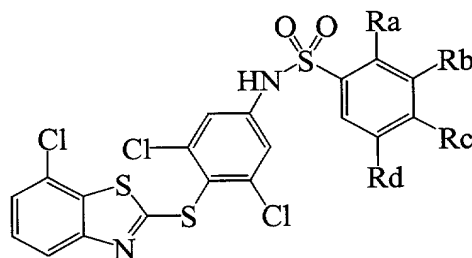
¹H NMR (DMSO) δ 8.587 (s, 2H), 7.852 (m, 1H), 7.54 (m 2H). Anal. calcd: 39.87 % C, 1.29 % H, 7.15 % N; found 39.62 %C, 1.21 % H, 7.00 % N.

Reduction of the nitro derivative (**76.1**) (0.92 g) by the method of example 32 gave the aniline (**76.2**) (0.76g) after flash chromatography.

¹H NMR (DMSO) δ 7.822 (d, J=8 Hz, 1H) 7.509 (t, J=8Hz, 1H), 7.465 (d, J=6.8 Hz, 1H) 6.882 (s, 2H), 6.529 (br s, 2H). MS (M+H) 361. Anal. calcd: 43.177 % C, 1.95 % H, 7.74 % N; found: 43.10 %C, 2.05 % H, 7.65 % N.

Reaction of the aniline **76.2** according to the method of example 3 with various sulfonyl chlorides gave the sulfonamides of Table 11.

Table 11



	Ra	Rb	Rc	Rd	m/e (M-H)
76.3	Cl	H	CF ₃	H	601
76.4	H	H	t-Bu	H	
76.5	Cl	H	Cl	H	567
76.6	Cl	H	H	H	535 (M+H)
76.7	H	H	H	H	
76.8	Cl	H	t-Bu	H	589
76.9	Cl	H	Me	H	547

Example 76.3

¹H NMR (DMSO) δ 11.96 (br s, 1H) 8.417 (d, J=8.4 Hz, 1H), 8.209 (s, 2H), 8.013 (d, J=8 Hz, 1H), 7.819 (d, J=6.8 Hz, 1H), 7.514 (m, 2 H), 7.411 (s, 2H). Anal.

calcd: 39.75 % C, 1.50 % H, 4.64 % N; found: 39.48 %C, 1.73 % H, 4.37 % N. MS (M-H) 601.

Example 76.4

5 Anal. calcd. for M+0.5 H₂O: 48.72 % C, 3.56 % H, 4.94 % N; found: 48.80 %C, 3.68 % H, 4.78 % N.

Example 76.5

10 ¹H NMR (DMSO) δ 11.83 (br s, 1H) 8.212 (d, J=8.4 Hz, 1H), 7.962 (d, J=2H, 1H), 7.827 (dd, J=6.8, 2 Hz, 1H), 7.723 (dd, J=8.5, 2.1 Hz, 1H), 7.518 (t, J=7.9 Hz, 1H), 7.492 (dd, J=7.8, 2.0 Hz, 1H), 7.385 (s, 2H). MS (M-H) 567. mp 216°C. Anal. calcd: 39.98% C, 1.59 % H, 4.91 % N; found: 39.81 %C, 1.59 % H, 4.85 % N.

Example 76.6

15 ¹H NMR (DMSO) δ 11.72 (br s, 1H), 8.222 (d, J=8 Hz, 1H), 7.822 (dd, J=7.2, 2.0 Hz, 1H), 7.730 (d, J=4 Hz, 2H), 7.636 (m, 1H), 7.516 (t, J=8 Hz, 1H), 7.490 (d, J=8 Hz, 1H), 7.379 (s, 2H). MS (M+H) 535.

Example 76.7

20 ¹H NMR (DMSO) δ 11.38 (br s, 1H), 8.906 (d, J=8 Hz, 2H), 7.827 (dd, J=7.2, 2.0 Hz, 1H), 7.721 (t, J=6.8 Hz, 1H), 7.655 (t, J=8 Hz, 2H), 7.519 (t, J=8 Hz, 1H), 7.493 (d, J=6.8 Hz, 1H), 7.412 (s, 2H).

Example 76.8

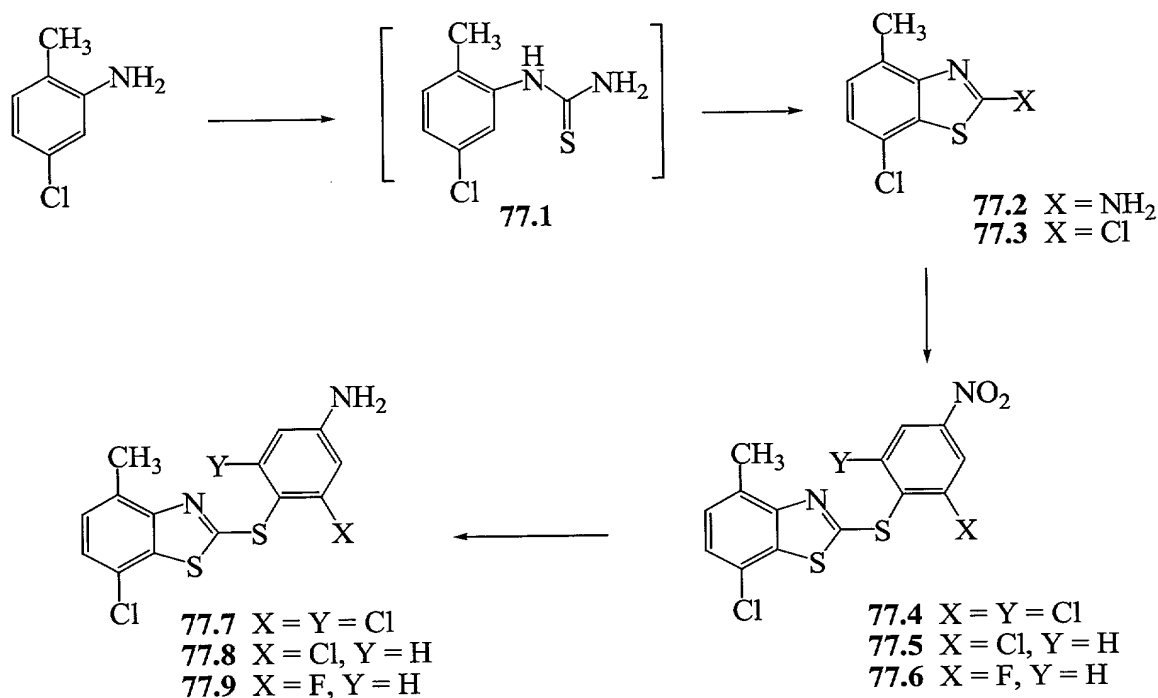
25 ¹H NMR (DMSO) δ 11.70 (1H, s), 8.13 (1H, d, 8.4), 7.80-7.87 (1H, m), 7.63-7.71 (2H, m), 7.48-7.55 (2H, m), 7.39 (2H, s). MS (M-H) 589. mp 131.3°C. Anal. calcd: C 46.63, H 3.06, N 4.73; found C 48.09, H 3.65, N 4.35

Example 76.9

30 ¹H NMR (DMSO) δ 11.70 (1H, s), 8.07-8.20 (1H, m), 7.80-7.93 (1H, m), 7.35-7.65 (6H, m). MS (M-H) 546.8. mp 220.9°C.

EXAMPLE 77

This example illustrates the preparation of anilines 77.7, 77.8 and 77.9



- 5 In analogy to the procedures of Weinstock et. al (*J. Med. Chem.* 30:1166-1176 (1987), conc. sulfuric acid (8.74 g) was added slowly to a solution of 5-chloro-2-methylaniline (25g) in chlorobenzene (120 mL) to form a thick slurry. Powdered NaSCN (18.6g) was added. The mixture was heated at 110°C for one hour then maintained at 50°C overnight. After dilution with hexane (300 mL), the solid was collected by
- 10 filtration, washed with hot water and rinsed with ethyl ether to afford 15.65g of intermediate thiourea 77.1 which was used directly in the next step.

Preparation of 2-amino-4-methyl-7-chlorobenzothiazole (77.2).

- 15 Bromine (25.44g) was added to a suspension of 77.1 (15g) in chloroform (110 mL) maintained below +10°C. After the addition was complete, the reaction was allowed to warm to RT then heated at reflux for 30 minutes. After cooling, the orange solid was collected by filtration and suspended in acetone (100mL) which discharges the remaining color. Solids were collected by filtration and rinsed with ethyl ether to afford the HBr salt.
- 20 ¹H NMR (DMSO) δ 7.182 (d, J=8 Hz, 1H), 7.137 (d, J=8 Hz, 1H), 2.40 (s, 3H).

The salt was suspended in water at 95°C. The pH of the suspension was adjusted to pH 9 with 0.5 N NaOH. After cooling, the solids were collected by filtration, rinsed with water and dissolved in ethylether/methylene chloride. The organic layer was dried over magnesium sulfate. After concentration, 2-amino-4-methyl-7-chlorobenzothiazole (**77.2**) (7.47g) was obtained as a white solid.

MS (M+H) 199. Anal. calcd.: 48.36 % C, 3.55 % H, 14.10 % N; found: 48.29 %C, 3.55 % H, 14.01 % N.

Preparation of 2-7-dichloro-4-methyl-benzothiazole (77.3)

To a slurry of 2-amino-4-methyl-7-chlorobenzothiazole(**77.2**) (6.37g) in H₃PO₄ (85%, 213 ml) in a 500 ml 3-necked flask with mechanical stirring and an internal temperature of < -10°C, was added dropwise a solution of NaNO₂ (6.87g) in water (11 ml). The mixture was warmed to 0° for 30 minutes and then recooled. The slurry was then slowly added to a cold (~-5°C) solution of CuSO₄•5 H₂O (32 g) and NaCl (40g) in water (128 ml) with vigorous mechanical stirring. After the foaming subsides and warming to RT, the solids were collected by filtration and rinsed with water. The solids were dissolved in ether leaving some insoluble residue. The ether solution was washed with water, and sodium bicarbonate solution. After the organic layer was concentrated, the residue was purified by flash chromatography with 10% methylene chloride in hexane to afford 2-chloro-4-methyl-7-chlorobenzothiazole (**77.3**) (4.48g).

¹H NMR (CDCl₃) δ 7.288 (d, J=8 Hz, 1H), 7.231 (dq, J=8. 0.8 Hz, 1H), 2.651 (d, J=0.8Hz, 3H). Anal. calcd.: 44.06 % C, 2.31 % H, 6.42 % N; found: 44.16 %C, 2.34 % H, 6.32 % N.

Coupling of **77.3** (0.65 g) with 3,5-dichloro-4-mercapto nitrobenzene by the method of example 73 gave after flash chromatography the nitro derivative **77.4** (0.97g) as a yellow solid.

¹H NMR (DMSO) δ 8.394 (s, 2H), 7.237 (d, J=8 Hz, 1H), 7.209 (d, J=8 Hz, 1H), 2.621 (s, 3H). MS (M+H) 405

Coupling of **77.3** (0.7 g) with 3-chloro-4-mercapto nitrobenzene by the method of example 73 gave the nitro derivative **77.5** (1.02 g) as a yellow solid.

¹H NMR (DMSO) δ 8.535 (br s, 1H), 8.261 (dd, J= 8.4, 2 Hz, 1H), 8.040 (d, J=8.4 Hz, 1H), 7.496 (d, J=8.4 Hz, 1H), 7.419 (d, J=8.4 Hz, 1H), 2.601 (s, 3H). MS (M+H) 371. Anal. calcd.: 45.40 % C, 2.18 % H, 7.57 % N; found: 45.25 %C, 2.23 % H, 7.49 % N.

Coupling of **77.3** (1.12 g) with 3-fluoro-4-mercapto nitrobenzene by the method of example 73 gave after flash chromatography the nitro derivative **77.6** (SY1904-2) (1.8 g) ^1H NMR

Reduction of **77.4** (0.96g) with tin dichloride by the method of example 32 gave the aniline (**77.7**) (0.84g) used directly in later reactions:

^1H NMR (DMSO) δ 7.352 (d, J=8 Hz, 1H), 7.322 (d, J=8 Hz, 1H), 6.884 (s, 2H), 6.533 (br s, 2H), 2.565 (s, 3H).

Reduction of **77.5** (1.13 g) with tin dichloride by the method of example 32 gave the aniline (**77.8**) (1.04 g) used directly in later reactions:

^1H NMR (DMSO) δ 7.543 (d, J=8.4 Hz, 1H), 7.329 (d, J=8 Hz, 1H), 7.301 (d, J=8 Hz, 1H), 6.889 (d, J=2 Hz, 1H), 6.663 (dd, J= 8.4, 2.4Hz, 1H), 6.231 (br s, 2H), 2.557 (s, 3H). MS (M+H) 341. Anal. calcd. for M+0.25 H₂O: 48.63 % C, 3.06 % H, 8.10 % N; found: 48.67 %C, 3.06 % H, 7.96 % N.

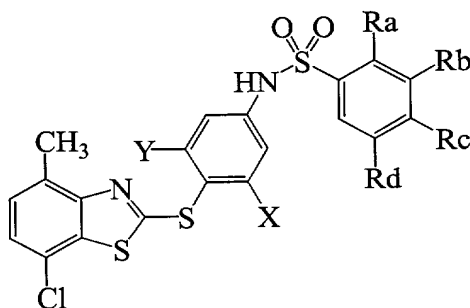
Reduction of **77.6** (1.75 g) with tin dichloride by the method of example 32 gave after chromatography the aniline (**77.9**) (1.2 g)

^1H NMR: δ 7.43 (1H, t, 8.3), 7.30-7.37 (2H, m), 6.53-6.58 (2H, m), 6.28 (2H, s).

EXAMPLE 78

Treatment of the anilines **77.7**, **77.8** or **77.9** by the method of example 3 with various sulfonyl chlorides gave the sulfonamides of Table 12.

Table 12



		X	Y	Ra	Rb	Rc	Rd	m/e (M-H)
25	78.1	Cl	Cl	Cl	H	Cl	H	581
	78.2	Cl	Cl	Cl	H	CF ₃	H	615
	78.3	Cl	Cl	Cl	H	Cl	Me	595
	78.4	Cl	H	Cl	H	CF ₃	H	581

78.5	Cl	H	Cl	H	Cl	H	565
78.6	F	H	Cl	H	CF ₃	H	565
78.7	F	H	Cl	H	Cl	H	531

5 Example 78.1

¹H NMR (DMSO) δ 11.813 (br s, 1H), 8.208 (d, J=8.8 Hz, 1H), 7.951 (d, J=2 Hz, 1H), 7.716 (dd, J=8.4, 2 Hz, 1H), 7.396 (s, 2H), 7.377 (d, J=8.4 Hz, 1H), 7.334 (d, J=8 Hz, 1H), 2.516 (s, 3H). MS (M-H) 581. Anal. calcd. for M+ H₂O: 39.85 % C, 2.17 % H, 4.65 % N; found: 40.10 %C, 1.89 % H, 4.57 % N.

10

Example 78.2

¹H NMR (DMSO) δ 11.975 (br s, 1H), 8.416 (d, J=8.4 Hz, 1H), 8.205 (br s, 1H), 8.012 (d, J=8 Hz, 1H), 7.423 (s, 2H), 7.376 (d, J=8 Hz, 1H), 7.332 (d, J=8 Hz, 1H), 2.512 (s, 3H). MS (M-H) 615. Anal. calcd.: 40.79 % C, 1.79 % H, 4.53 % N; found: 41.05 %C, 1.86 % H, 4.57 % N.

15

Example 78.3

¹H NMR (DMSO) δ 11.748 (s, 1H), 8.233 (s, 1H), 7.880 (s, 1H), 7.407 (s, 2H), 7.370 (d, J=8 HZ, 1H), 7.330 (d, J=8 Hz, 1H), 2.408 (s, 3H). MS (M-H) 595. Anal. calcd.: 42.12 % C, 2.19 % H, 4.68 % N; found: 41.84 %C, 2.23 % H, 4.51 % N.

20

Example 78.4

¹H NMR (DMSO) δ 11.73 (1H, s), 8.38 (1H, d, J= 8.3 Hz), 8.19 (1H, s), 7.99 (1H, d, J= 8.3 Hz), 7.88 (1H, d, J= 8.6 Hz), 7.45 (1H, d, J= 2.3 Hz), 7.23-7.40 (3H, m). MS (M-H) 580.8 (M-H). mp 189.0 °C.

25

Example 78.5

¹H NMR (DMSO) δ 11.57 (1H, s), 8.17 (1H, d, J= 8.6 Hz), 7.92 (1H, d, J= 2.1 Hz), 7.78 (1H, d, J= 8.5 Hz), 7.69 (1H, dd, J= 8.6, 2.1 Hz), 7.43 (1H, d, J= 2.3 Hz), 7.30-7.38 (2H, m), 7.25 (1H, dd, J= 8.6, 2.4 Hz). MS (M-H) 546.9. mp 218.1 °C.

30

Example 78.6

^1H NMR: δ 8.04 (1H, d, 8.3), 8.18 (1H, s), 7.99 (1H, d, 8.3), 7.80 (1H, t, 8.3), 7.30-7.40 (2H, m), 7.10-7.22 (2H, m). MS (M-H) 565.0. mp 221.2°C. Anal. calcd.: C 44.45, H 2.13, N 4.94; found C 44.01, H 2.18, N 4.67.

5

Example 78.7

^1H NMR (DMSO) δ 11.60 (1H, s), 8.18 (1H, d, 8.6), 7.91 (1H, d, 2.0), 7.79 (1H, t, 8.4), 7.69 (1H, dd, 8.6, 2.1), 7.30-7.40 (2H, m), 7.10-7.20 (2H, m). MS (M-H) 530.9. mp 230.4°C. Anal. calcd.: C 44.99, H 2.27, N 5.25; found C 44.49, H 2.26, N 5.08.

10

EXAMPLE 79

This example illustrates the preparation of compounds 79.1 to 79.7.

To a solution of 5-chloro-2-mercaptobenzothiazole (Acros) (2g), KOH (630 mg) in water (8 mL) at 100° C was added a solution of 3,4-dichloronitrobenzene (1.88g) in n-propanol (24 mL). The mixture was heated at reflux for 72 hrs. After cooling, the solids were collected by filtration and rinsed with water. The solids were dried under vacuum to afford the nitro derivative 79.1 (2.25 g) as a yellow solid used directly in the next step.

15

^1H NMR (DMSO) δ 8.54 (d, J=2.4 Hz, 1H), 8.26 (dd, J=8.6, 2.4 Hz, 1H), 8.123 (d, J=8.6 Hz, 1H), 8.08 (d, J=1.9 Hz, 1H), 8.03 (d, J=8.7 Hz, 1H), 7.533 (dd, J=8.6, 2.1).

Reduction of 79.1 (2.2 g) with tin dichloride by the method of example 32 gave after work-up the aniline (79.2) (1.2 g) which was used directly in later reactions.

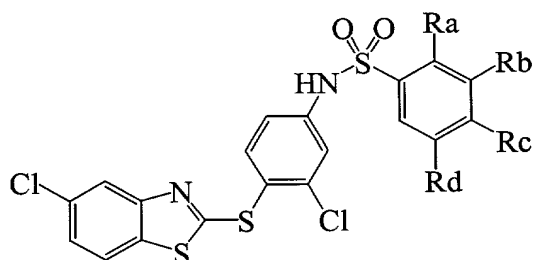
25

^1H NMR (DMSO) δ 7.94 (d, J=8.4 Hz, 1H), 7.891 (d, J=1.6 Hz, 1H), 7.537 (d, J=8.4 Hz, 1H), 7.371 (dd, J=8.4, 2.1 Hz, 1H), 6.877 (d, J=2.4 Hz, 1H), 6.651 (dd, J=8.4, 2.4 Hz, 1H), 6.203 (s, 2H). MS (M+H) 327

Treatment of the aniline 79.2 by the method of example 3 with various sulfonyl chlorides gave the sulfonamides of Table 13.

30

Table 13



		Ra	Rb	Rc	Rd	m/e (M-H)
5	79.3	Cl	H	Cl	Me	547
	79.4	Cl	H	Cl	H	533 (M+H)
	79.5	Cl	H	CF ₃	H	567
	79.6	H	Cl	Cl	H	533
	79.7	Me	H	Cl	Me	527

10 **Example 79.3**

¹H NMR(DMSO) δ 11.52 (1H, s), 8.20 (1H, s), 7.84-8.00 (4H, m), 7.35-7.43 (2H, m), 7.22 (1H, d, *J* = 8.5 Hz), 2.41 (3H, s). MS (M-H) 546.8. mp 203.7 °C.

Example 79.4

15 ¹H NMR(DMSO) δ 11.57 (1H, s), 8.18 (1H, d, *J* = 8.5 Hz), 7.90-7.98 (2H, m), 7.86 (1H, d, *J* = 8.5 Hz), 7.72 (1H, d, *J* = 8.7 Hz), 7.37-7.43 (2H, m), 7.22 (1H, d, *J* = 8.8 Hz). MS (M+H) 532.8. mp 174.7 °C.

Example 79.5

20 ¹H NMR(DMSO) δ 8.38 (1H, d, 8.4 Hz), 8.21 (1H, s), 8.01 (1H, d, *J* = 8.2 Hz), 7.90-7.96 (2H, m), 7.86 (1H, d, *J* = 7.7 Hz), 7.42 (2H, s), 7.23 (1H, d, *J* = 8.6 Hz). MS (M-H) 566.9. mp 158.8 °C.

Example 79.6

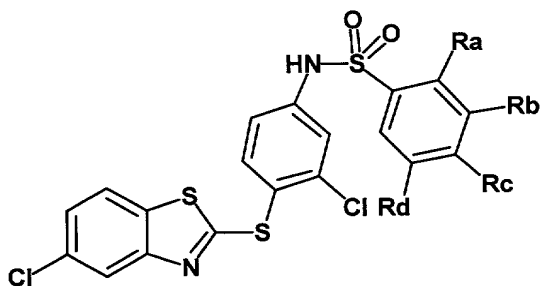
25 ¹H NMR(DMSO) δ 11.25 (1H, s), 8.06 (1H, d, *J* = 1.5 Hz), 7.80-7.96 (5H, m), 7.40-7.46 (2H, m), 7.27-7.32 (1H, m). MS (M-H) 532.8. mp 201.2 °C.

Example 79.7

^1H NMR(DMSO) δ 11.30 (1H, s), 8.00 (1H, s), 7.90-7.98 (2H, m), 7.84 (1H, d, $J = 8.6$ Hz), 7.57 (1H, s), 7.35-7.44 (2H, m), 7.18-7.23 (1H, m), 2.57 (3H, s), 2.37 (3H, s). mp 205.1 $^{\circ}\text{C}$.

5

Table 14



		Ra	Rb	Rc	Rd	m/e (M-H)
	79.3	Cl	H	Cl	Me	547
10	79.4	Cl	H	Cl	H	533 (M+H)
	79.5	Cl	H	CF ₃	H	567
	79.6	H	Cl	Cl	H	533
	79.7	Me	H	Cl	Me	527
	79.8	Cl	H	Me	H	513
15	79.9	Cl	H	t-Bu	H	555

Example 79.8

^1H NMR (d_6 -DMSO) δ 11.43 (1H, s), 8.08 (1H, d, $J = 8.0$ Hz), 7.90-8.00 (2H, m), 7.85 (1H, d, $J = 8.5$ Hz), 7.57 (1H, s), 7.37-7.47 (3H, m), 7.21 (1H, d, $J = 8.4$ Hz), 2.38 (3H, s). MS (M-H) 512.9. mp 201.0 $^{\circ}\text{C}$. Anal. calcd.; C 46.56, H 2.54, N 5.43; found C 46.93, H 2.58, N 5.40.

20

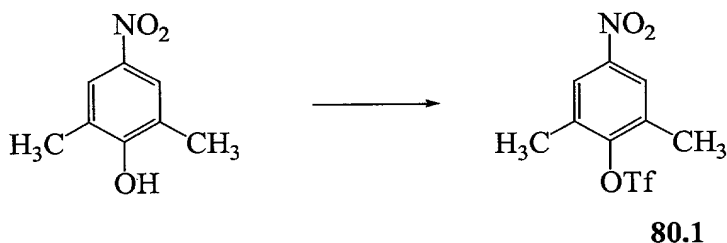
Example 79.9

^1H NMR (d_6 -DMSO) δ 11.44 (1H, s), 8.10 (1H, d, $J = 8.3$ Hz), 7.90-7.97 (2H, m), 7.86 (1H, d, $J = 8.6$ Hz), 7.60-7.68 (2H, m), 7.37-7.43 (2H, m), 7.23 (1H, dd, $J = 8.5, 2.4$ Hz), 1.29 (9H, s). MS (M-H) 554.9. mp 177.8 $^{\circ}\text{C}$. Anal. calcd.; C 49.51, H 3.43, N 5.02; found C 49.67, H 3.44, N 4.97.

25

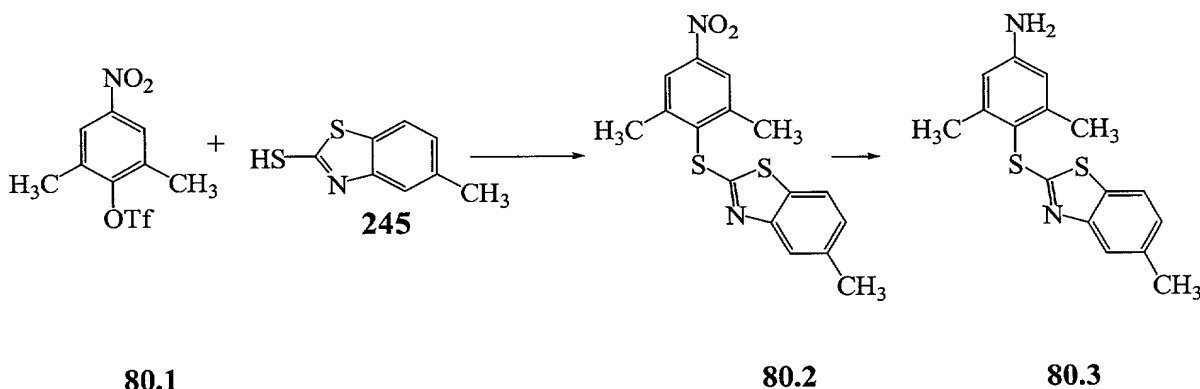
EXAMPLE 80

This illustrates the synthesis of compound **80.4**.



2,6-dimethyl-4-nitrophenol (4.93 g, 29.5 mmol) was suspended in anhydrous CH_2Cl_2 (30 mL). Hünig's base (12.4 mL, 70 mmol) was added to give a homogeneous, dark red solution. The reaction mixture was cooled to -15°C and triflic anhydride (10 g, 35 mmol) was slowly added. The very dark reaction mixture was stirred at -15°C for 15 minutes, then poured into 3N HCl (100 mL). The layers were separated and the aqueous layer was extracted 1 x 150 mL CH_2Cl_2 . The combined organic layers were washed 1 x 50 mL sat. brine, dried over MgSO_4 , and concentrated to a dark red oil. This oil was filtered through a 2 cm plug of silica gel (eluting with 3:1 hexanes:ethyl acetate) and concentrated to an orange oil which was diluted with 10 mL of hexanes and allowed to stand at room temperature until crystallization of the product took place. The crystals were collected and dried under vacuum. The mother liquor was concentrated, then diluted with 5 mL of CH_2Cl_2 and 25 mL of hexanes and again allowed to stand until crystallization was complete. The second crop was collected by filtration and dried under vacuum. Combined yield of the two crops was 7.87 g of triflate **80.1**.

$^1\text{H NMR}$ (CDCl_3) δ 8.03 (s, 2H); 2.50 (s, 6H).



20

25

5-methyl-2-mercaptobenzothiazole (1.45 g, 8 mmol) was suspended in anhydrous THF (3.5 mL). A solution of potassium *tert*-butoxide (7.35 mL, 1.0 N in THF) was added in one portion. The very thick precipitate of the mercaptobenzothiazole potassium salt was dissolved by addition of DMF (1 mL). Triflate **80.1** (2 g, 6.7 mmol)

was dissolved in DMF (1 mL) and added to the reaction mixture which was then heated to 50 °C for 16 h. The reaction mixture was pouted into 100 mL DI water and extracted 2 x 50 mL of ethyl acetate. The combined organic layers were washed with sat. brine, dried over MgSO₄, filtered, concentrated, and the residue purified by flash chromatography (silica gel, 19:1 to 4:1 hexanes:ethyl acetate). Fractions containing the desired product were concentrated and the residue recrystallized from hot hexanes:ethyl acetate. Filtration and drying provided the S-arylated compound **80.2** as bright yellow crystals (0.90 g).

¹H NMR (CD₃CN) δ 8.12 (s, 2H); 7.68 (d, 1H); 7.61 (s, 1H); 7.17 (d, 1H); 2.60 (s, 6H); 2.42 (s, 3H). MS (M+H) 331.1

Reduction of **80.2** (0.88 g) by the method of Example 32 gave aniline **80.3** (0.4 g) as a solid.

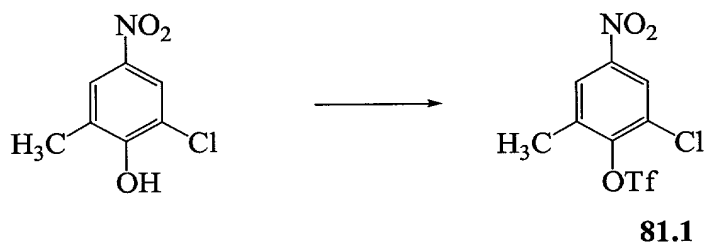
¹H NMR (CDCl₃) δ 7.723 (m, 1H), 7.598 (s, 1H), 7.122 (d, J=8.4Hz, 1H), 6.706 (s, 2H), 5.304 (br, 2H), 2.399 (s, 3H), 2.338 (s, 6H)

Sulfonylation of **80.3** (400 mg) by the method of example 3 gave **80.4** (Table 15)(0.36 g).

¹H NMR (DMSO) δ 11.284 (s, 1H), 8.369 (d, J=8.2Hz, 1H), 8.170 (s, 1H), 7.969 (d, J=8.2 Hz, 1H), 7.676 (d, J=8.2 Hz, 1H), 7.591 (s, 1H), 7.126 (d, J=8.2Hz, 1H), 7.056 (s, 2H), 2.372 (s, 3H), 2.326 (s, 6H). MS (M+H) 543

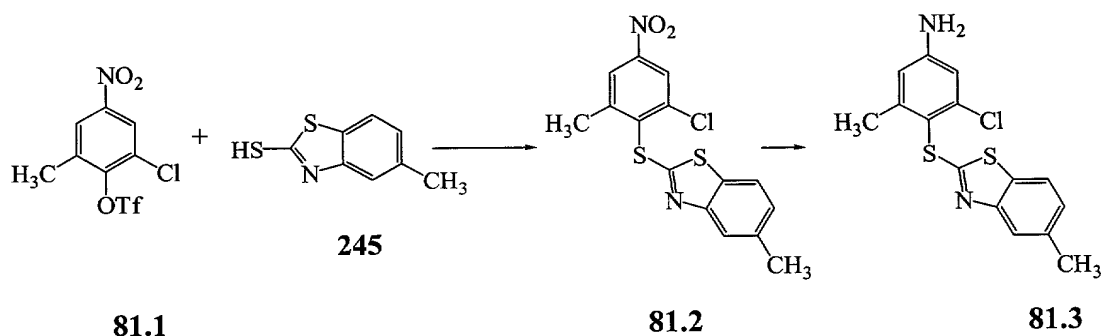
EXAMPLE 81

This illustrates the synthesis of compound **81.4**.



2-chloro-6-methyl-4-nitro-phenol (2.5 g, 13.3 mmol) was converted to triflate **81.1** according to the method given in Example 80. Triflate **81.1** was an oil and could not be recrystallized. 4.0 g of triflate **81.1** was obtained.

¹H NMR (CD₃CN) δ 8.24 (d, 1H); 8.77 (d, 1H); 2.56 (s, 3H).



5-methyl-2-mercaptobenzothiazole (1.36 g, 7.5 mmol) and triflate **81.1** (2 g, 6.26 mmol) were reacted according to the procedure given in Example **80**. S-arylated compound **81.2** was obtained as bright yellow crystals (1.2 g). This product contained a minor amount of a contaminant of unknown structure. This contaminant had no effect on subsequent reactions, nor was it found in subsequent products.

¹H NMR (CD₃CN) δ 8.28 (d, 1H); 8.14 (d, 1H); 7.67 (s, 1H); 7.56 (d, 1H); 7.14 (d, 1H); 2.68 (s, 3H); 2.45 (s, 3H). MS (M+H) 351.

Reduction of **81.2** (0.88 g) by the method of Example 32 gave aniline **81.3** (0.4 g) as a solid.

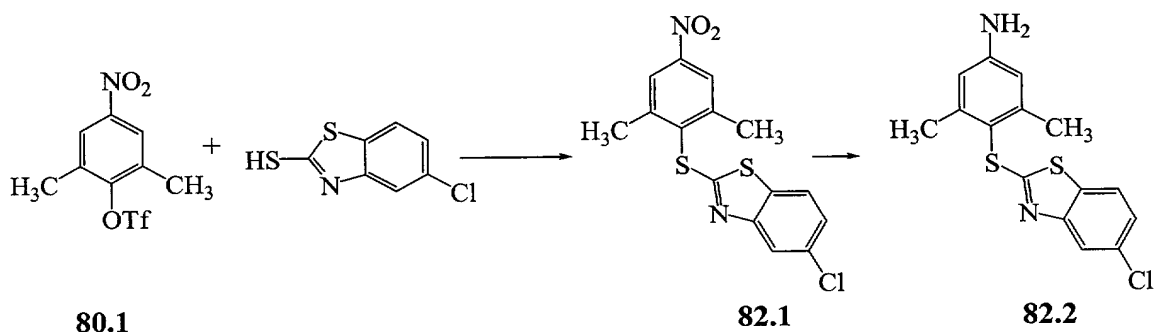
¹H NMR (DMSO) δ 7.740 (d, J=8 Hz, 1H), 7.608 (s, 1H), 7.131 (d, J=8 Hz, 1H), 6.732 (d, J=2.6 Hz, 1H), 6.588 (d, J=2.6 Hz, 1H), 6.048 (s, 2H), 2.403 (s, 3H), 2.334 (s, 3H).

Sulfonylation of **81.3** by the method of example 3 gave **81.4** (see Table 15).

¹H NMR (DMSO) δ 11.610 (s, 1H), 8.398 (d, J=8.4 Hz, 1H), 8.210 (s, 1H), 8.005 (d, J=8.4Hz, 1H), 7.730 (d, J=8Hz 1H), 7.621 (s, 1H), 7.7.276 (d, J=2.8Hz, 1H), 7.167 (m, 2H), 2.409 (s, 3H), 2.397 (s, 3H).

EXAMPLE 82

This illustrates the synthesis of compound **82.3**.



5-chloro-2-mercaptobenzothiazole (202 mg, 1 mmol) and triflate **80.1** (270 mg, 0.9 mmol) were reacted according to the procedure given in Example **80**. S-arylated compound **82.1** was obtained as a light yellow solid (203 mg).

¹H NMR (CDCl₃) δ 8.09 (s, 2H); 7.83 (d, 1H); 7.56 (d, 1H); 7.26 (dd, 1H); 2.63 (s, 3H). MS (M+H) 351.0

Reduction of **82.1** (0.7 g) by the method of example 32 gave aniline **82.2** (0.62 g).

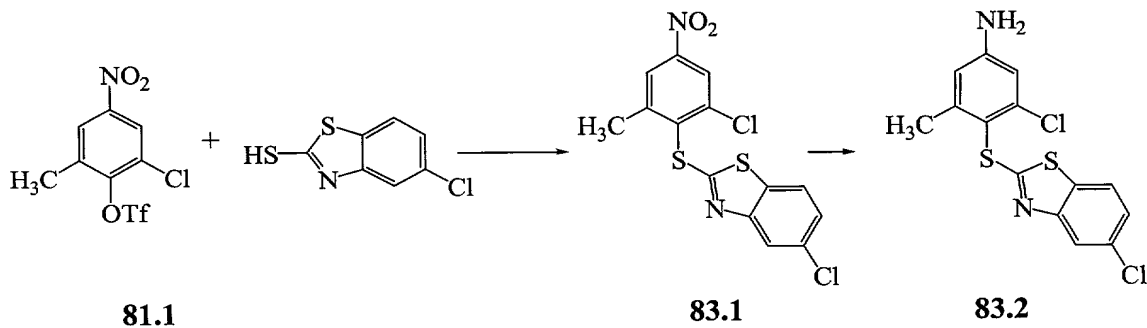
¹H NMR (DMSO) δ 7.884 (d, J=8.4 Hz, 1H), 7.846 (d, J=2 Hz, 1H), 7.329 (dd, J=8.4, 2 Hz, 1H), 6.495 (s, 2H), 5.669 (s, 2H), 2.283 (s, 3H). MS (M+H) 321

Sulfonylation of **82.2** by the method of example 3 gave **82.3** (see Table 15).

15 ¹H NMR (DMSO) δ 11.304 (s, 1H), 8.377 (d, J=8 Hz, 1H), 8.180 (d, J=1.2 Hz, 1H), 7.980 (br d, J=8.4, 1H), 7.874 (d, J=2.4 Hz, 1H), 7.866 (d, J=8 Hz, 1H), 7.365 (dd, J=8.4, 2 Hz, 1H), 7.068 (br s, 2H), 2.341 (s, 3H). MS (M-H) 561

EXAMPLE 83

20 This illustrates the synthesis of compound 83.3.



5-chloro-2-mercaptobenzothiazole (0.76 g, 3.75 mmol) and triflate **81.1** (1.0 g, 3.44 mmol) were reacted according to the procedure given in Example 80. S-arylated compound **83.1** was obtained as a light yellow solid (0.83 g).

¹H NMR (CDCl₃) δ 8.30 (s, 1H); 8.17 (s, 1H); 7.85 (s, 1H); 7.61 (d, 1H); 7.30 (d, 1H); 2.71 (s, 3H). MS (M+H) 371

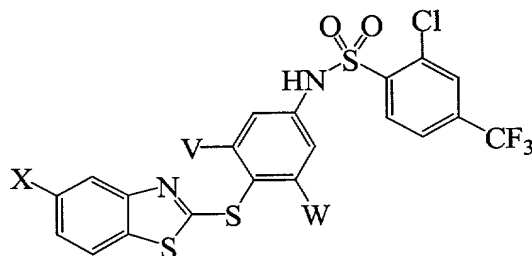
Reduction of **83.1** (0.8 g) by the method of Example 32 gave aniline **83.2** (0.47 g).

¹H NMR (DMSO) δ 7.918 (d, J=8.8 Hz, 1H), 7.874 (d, J=2 Hz, 1H), 7.356 (dd, J=8.4, 2 Hz, 1H), 6.745 (d, J=2.4 Hz, 1H), 6.600 (d, J=2 Hz, 1H), 6.089 (br s, 2H), 2.336 (s, 3H). MS (M+H) 341.

Sulfonylation of **83.2** by the method of example 3 gave **83.3** (see Table 15).

¹H NMR (DMSO) δ 11.647 (s, 1H), 8.407 (d, J=8.4 Hz, 1H), 8.213 (br s, 1H), 8.008 (br d, J=8.4, 1H), 7.910 (d, J=8 Hz, 1H), 7.90 (s, 1H), 7.396 (d, J=8.8 Hz, 1H), 7.290 (br s, 1H), 7.188 (br s, 1H), 2.416 (s, 3H). MS (M-H) 581.

Table 15

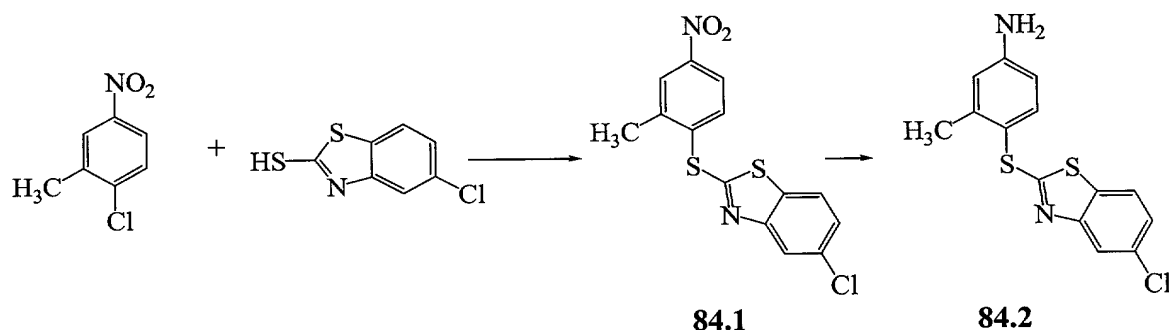


		X	V	W	m/e (M-H)
20	80.4	Me	Me	Me	543 (M+H)
	81.4	Me	Me	Cl	
	82.3	Cl	Me	Me	561
	83.3	Cl	Me	Cl	581
	84.3	Cl	H	Me	547

25

EXAMPLE 84

This illustrates the synthesis of compound **84.3**



Sodium hydride (1g, 60% in oil) was added to a solution of 5-chloro-2-mercaptobenzothiazole (5.4 g) in DMF (50 mL). After gas evolution had subsided a solution of 2-chloro-5-nitro toluene in DMF was added and the mixture heated at 60°C for 2 days. After cooling, the solution was filtered. The filtrate was diluted with water and extracted into ethyl ether. The organic layer was concentrated to a brown oil which was treated with hexane to form a solid precipitate which was collected by filtration as **84.1** (0.624 g).

¹H NMR (DMSO) δ 8.372 (d, J=2.4 Hz, 1H), 8.171 (dd, J=8.8, 2.4 Hz, 1H), 8.027 (d, J=8.8 Hz, 1H), 8.003 (d, J=8 Hz, 1H), 7.988 (d, J=2 Hz, 1H), 7.454 (dd, J=8.4, 1.6 Hz, 1H), 2.553 (s, 3H).

Reduction of **84.1** (0.6 g) with SnCl₂ by the method of example 32 gave after chromatography **84.2** (0.48 g) as a solid.

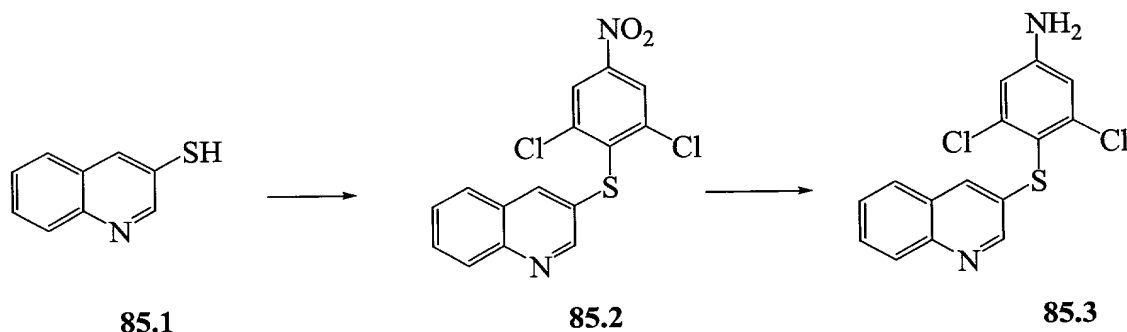
¹H NMR (DMSO) δ 7.899 (d, J=8.8 Hz, 1H), 7.853 (d, J=2 Hz, 1H), 7.345 (d, J=8.4 Hz, 1H), 7.336 (dd, J=8.4, 2 Hz, 1H), 6.631 (d, J=2 Hz, 1H), 6.531 (dd, J=8.4, 2 Hz, 1H), 5.766 (br s, 2H). MS (M+Na) 329

Sulfonylation of **84.2** (0.4 g) by the method of example 3 gave **84.3** (Table 15) (0.66 g) as a foam.

¹H NMR (DMSO) δ 11.376 (s, 1H), 8.355 (d, J=8 Hz, 1H), 8.180 (d, J=1.2 Hz, 1H), 7.983 (dd, J=8.4, 2 Hz, 1H), 7.893 (d, J=9.2 Hz, 1H), 7.88 (s, 1H), 7.656 (d, J=8.4 Hz, 1H), 7.377 (dd, J=8.8, 1.6 Hz, 1H), 7.211 (d, J=2.8 Hz, 1H), 7.108 (dd, J=8.4, 2 Hz, 1H), 2.334 (s, 3H). MS (M-H) 547

EXAMPLE 85

This illustrates the synthesis of compound **85.3**



Compound **85.1** was prepared by a modification of the published
 5 procedure of Albert and Barlin (J. Chem. Soc. 2384-2396 (1959). 3-Aminoquinoline
 (15.0 g, 105 mmol) was suspended in a mixture of 10N HCl (40 mL), ice (21g) and water
 (100 mL) at 0-5 °C, before sodium nitrite (7.6 g, 110 mmol) was added slowly. The
 mixture was then added portionwise to another solution of potassium ethyl xanthate (20.8
 g, 125 mmol) in water (60 mL) at 45 °C. The mixture was heated for 1 hr before cooling
 10 off. The mixture was then extracted with ether. The ethereal solution was washed with
 2N NaOH solution, water, and brine before drying over magnesium sulfate. After
 filtration, the removal of the solvent gave a brown oil (15g), which was then dissolved in
 ethanol (150 mL) and refluxed with KOH (25g) under nitrogen overnight. The ethanol
 solvent was then removed under vacuum, and the residue was separated between water
 15 and ether. The ethereal solution was discarded. The aqueous solution was acidified to
 pH = ~4, before it was extracted with ether. Then ethereal solution was washed with
 brine, dried over magnesium sulfate, filtered and concentrated under vacuum to give
 crude product (7.5g) as a brown oil. Subsequent flash chromatography with eluent (0%-
 5%-10% ethyl acetate / dichloromethane) produced 3-mercaptoquinoline (**85.1**) (5.35g,
 20 32% yield) as a solid.

¹H NMR (DMSO) δ 9.02 (1H, d, *J* = 2.3 Hz), 8.63 (1H, d, *J* = 2.2 Hz),
 7.95-8.05 (2H, m), 7.75-8.02 (1H, m), 7.60-7.67 (1H, m).

To a mixture of 3-mercaptoquinoline (**85.1**) (1.18 g, 7.33 mmol) and 1,2,3-
 chloro-5-nitrobenzene (1.66 g, 7.33 mmol) dissolved in ethanol (100 mL), was added a
 25 THF solution of *t*-BuOK (7.5 mL, 1M). The mixture was then heated at 80 °C overnight
 before cooling off. After the removal of ethanol solvent, the mixture was separated
 between ethyl acetate and water. The organic solution was washed with brine, dried over
 magnesium sulfate and filtered. The filtrate was then concentrated to give a crude

product, which was then flash chromatographed with eluent (10% hexanes / dichloromethane) to afford **85.2** (1.80 g, 70% yield) as a yellow oil.

^1H NMR (DMSO) δ 8.75 (1H, d, $J = 2.3$), 8.51 (1H, s), 8.22 (1H, s), 8.01 (1H, d, $J = 8.4$ Hz), 7.92 (1H, d, $J = 7.6$ Hz), 7.74-7.80 (1H, m), 7.60-7.66 (1H, m).

5 An ethyl acetate solution (100 mL) of **85.2** (1.80 g, 5.1 mmol) and tin chloride (II) dihydrate (6.88 g, 30 mmol) was heated at reflux overnight before cooling off. The solution was then poured into 1N NaOH solution (400 mL). After stirring for 30 min, the mixture was separated, and the organic solution was washed with water, saturated sodium bicarbonate and brine. After drying over magnesium sulfate, the
10 solution was filtered and concentrated under vacuum. The residue was mixed with dichloromethane (10 mL) and sonicated. Subsequent vacuum filtration provided the aniline **85.3** (1.35g, 82% yield) as an off-white solid.

^1H NMR (DMSO) δ 8.61 (1H, d, $J = 2.4$), 7.96 (1H, d, $J = 8.4$ Hz), 7.88 (1H, d, $J = 8.2$ Hz), 7.83 (1H, d, $J = 2.2$ Hz), 7.67-7.72 (1H, m), 7.54-7.60 (1H, m). mp
15 213.2 °C.

EXAMPLE 86

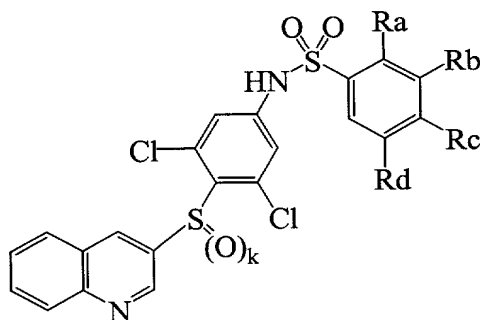
This illustrates the synthesis of compound **86** (see Table 16).

The aniline **85.3** (250 mg, 0.78 mmol) and 2-chlorobenzenesulfonyl chloride (339 mg, 1.60 mmol) were dissolved in a mixed solvent of THF (5 mL) and
20 dichloromethane (5 mL). To the solution was added pyridine (0.185 mL, 2.34 mmol) and catalytic amount of DMAP. The solution was heated at 50 °C to distill off dichloromethane, and then THF with assistance of vacuum. The residue was flash chromatographed with eluent (2.5% ethyl acetate / dichloromethane) to give sulfonamide
25 **86** (302 mg, 78%) as an off-white solid.

^1H NMR(DMSO) δ 11.58 (1H, s), 8.61 (1H, d, $J = 2.4$ Hz), 8.19 (1H, d, $J = 7.6$ Hz), 7.83-8.00 (3H, m), 7.67-7.75 (3H, m), 7.56-7.65 (2H, m), 7.31 (2H, s). MS (M+H) 494.9. mp: 219.6 °C. Anal. calcd: C 50.87, H 2.64, N 5.65; found C 50.86, H 2.62, N 5.52.

The compounds of Table 16 were prepared by the method of example 86
30 from compound **84.3** and the corresponding arylsulfonyl chloride.

Table 16



		k	R _a	R _b	R _c	R _d	m/e (M+H)
5	86	0	Cl	H	H	H	495
	87.1	0	Cl	H	Cl	H	529
	87.2	0	H	H	H	H	461
	87.3	0	Cl	H	CF ₃	H	561 (M-H)
	88.1	1	Cl	H	H	H	511
10	88.2	1	Cl	H	Cl	H	543 (M-H)
	88.3	1	H	H	H	H	477

EXAMPLE 87

Example 87.1

¹H NMR(DMSO) δ 11.66 (1H, broad), 8.63 (1H, d, *J* = 2.3 Hz), 8.18 (1H, d, *J* = 8.6 Hz), 7.85-8.00 (4H, m), 7.70-7.75 (2H, m), 7.57-7.62 (1H, m), 7.32 (2H, s). MS (M+H) 529.0. mp 214.0 °C. Elemental Analysis: theory C 47.56, H 2.28, N 5.28; Found C 47.30, H 2.36, N 5.37.

Example 87.2

¹H NMR(DMSO): δ 11.22 (1H, s), 8.61 (1H, d, *J* = 2.3 Hz), 7.82-7.98 (5H, m), 7.57-7.75 (5H, m), 7.34 (2H, s). MS (M+H) 461.0. mp 246.8 °C. Elemental Analysis theory C 54.67, H 3.06, N 6.07; found C 54.71, H 3.05, N 5.94.

Example 87.3

¹H NMR (DMSO) δ 11.70-12.00 (1H, broad), 8.60-8.67 (1H, m), 8.35-8.43 (1H, m), 8.20-8.25 (1H, m), 7.56-8.06 (6H, m), 7.32-7.38 (2H, m). MS (M-H) 560.9. mp: 225.1 °C. Elemental Analysis: theory C 46.86, H 2.15, N 4.97; found C. 47.01, H 2.26, N 4.98.

EXAMPLE 88

General procedure for sulfur oxidation to the sulfoxide:

A naphthylthioether of examples 86 or 87 (0.2 mmol) was dissolved in a mixed solvent of dichloromethane (10 mL) and methanol (5 mL). To the solution was added mCPBA (120 mg, 0.7 mmol, 77% pure) in six batches over 20 minute intervals. Then the solution was washed with 5% sodium thiosulfate solution, 1% sodium bicarbonate solution and brine and then dried over magnesium sulfate. After filtering, the filtrate was concentrated to give a crude product, which was then flash chromatographed with eluent (5%-30% ethyl acetate / dichloromethane) to afford the corresponding sulfoxide.

Example 88.1

^1H NMR (DMSO): δ 11.75 (1H, s), 8.82 (1H, s), 8.68 (1H, s), 8.15-8.20 (2H, m), 8.09 (1H, d, $J = 8.5$ Hz), 7.85-7.91 (1H, m), 7.67-7.75 (3H, m), 7.57-7.64 (1H, m), 7.17 (2H, s). MS (M+H) 511. mp 239.5 °C with decomposition. Elemental Analysis: theory C 49.28, H 2.56, N 5.47; found C 49.30, H 2.63, N 5.37.

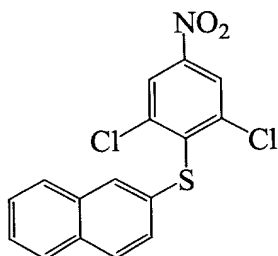
Example 88.2

^1H NMR(DMSO): δ 11.5-12.0 (broad), 8.83 (1H, s), 8.68 (1H, s), 8.15-8.20 (2H, m), 8.09 (1H, d, $J = 8.5$ Hz), 7.85-7.92 (2H, m), 7.55-7.75 (2H, m), 7.17 (2H, s). MS (M-H) 542.9. mp: 234.4. Elemental Analysis: theory C 46.17, H 2.21, N 5.13; found C 45.97, H 2.26, N 4.92.

Example 88.3

^1H NMR(DMSO) δ 11.43 (1H, s), 8.81 (1H, s), 8.68 (1H, s), 8.18 (1H, d, $J = 8.2$ Hz), 8.09 (1H, d, $J = 8.5$ Hz), 7.82-7.90 (3H, m), 7.58-7.74 (4H, m), 7.21 (2H, s). MS (M+H) 476.9. mp 261.8 °C with decomposition. Elemental Analysis: theory C 52.83, H 2.96, N 5.87; found C 52.71, H 3.05, N 5.71.

EXAMPLE 89

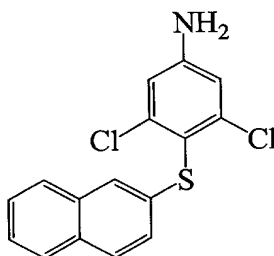


2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-naphthalene (89)

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-naphthalene was synthesized (100%) from 3,4,5-trichloronitrobenzene (Acros) and naphthalene-2-thiol (Avocado) in a similar manner as described in example 1 using DMSO as solvent instead of DMF.

^1H NMR (DMSO- d_6) δ 8.48 (s, 2H), 7.95-7.85 (m, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.85-7.8 (m, 1H), 7.75 (d, J = 1.8 Hz, 1H), 7.55-7.45 (m, 2H), 7.25 (dd, J = 8.7, 2.0 Hz, 1H).

EXAMPLE 90

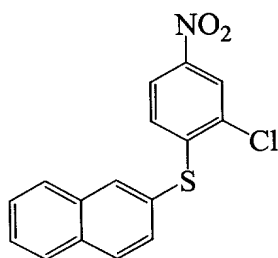


3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90)

To a 0.1M solution 2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-naphthalene (89) (774 mg, 2.2 mmol), in EtOAc was added tin(II)chloride dihydrate, obtained from Aldrich, (2.49 g, 11.05 mmol). The resulting mixture was refluxed for 2 hour. The crude reaction mixture was cooled to ambient temperature and excess 2M aqueous NaOH was added and allowed to stir for 15 minutes. Solid tin salts precipitated from the solution, were filtered off through a pad of celite and washed with EtOAc (200 mL). The organic layer was washed twice with brine (200 mL), dried over Na_2SO_4 , and concentrated under vacuum to yield 592 mg (84%) of (90) which was used without further purification.

^1H NMR (DMSO- d_6) δ 7.88-7.82 (m, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.5-7.4 (m, 3H), 7.13 (dd, J = 8.7, 1.9 Hz, 1H), 6.83 (s, 2H), 6.21 (s, 2H). MS (M-H) 318.

EXAMPLE 91

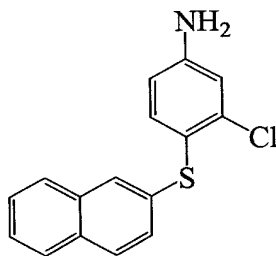


2-(2-Chloro-4-nitro-phenylsulfanyl)-naphthalene (91)

2-(2-Chloro-4-nitro-phenylsulfanyl)-naphthalene was synthesized (100%)
5 from 3-chloro-4-fluoro-nitrobenzene (Aldrich) and naphthalene-2-thiol (Avocado) in a similar manner as described in example 89.

^1H NMR (DMSO- d_6) δ 8.4-8.34 (m, 2H), 8.14 (d, J = 8.6 Hz, 1H), 8.09-8.0 (m, 3H), 7.72-7.6 (m, 3H), 6.88 (d, J = 8.9 Hz, 1H).

EXAMPLE 92

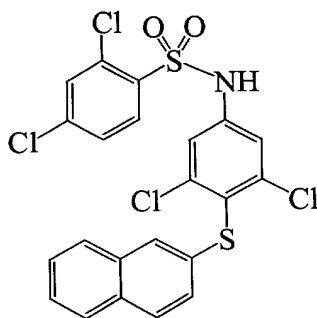


3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine

3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (**92**) was synthesized
(97%) from 2-(2-Chloro-4-nitro-phenylsulfanyl)-naphthalene (**91**) in a similar manner as
15 described in example 90.

^1H NMR (DMSO- d_6) δ 7.88-7.8 (m, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.5-7.42 (m, 3H), 7.35 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.6, 1.8 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 6.6 (dd, J = 8.4, 2.4 Hz, 1H). MS (M+H) 286

EXAMPLE 93

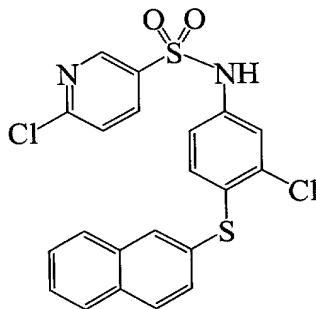


2,4-Dichloro-N-[3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-benzenesulfonamide (93)

5 To a 0.4M solution of 3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90)(153 mg, 0.48 mmol) in THF was added pyridine, obtained from aldrich, (0.19 mL, 2.4 mmol) followed by 2,4-dichlorobenzenesulfonyl chloride, obtained from Maybridge, (129 mg, 0.53 mmol). The resulting mixture was stirred for 6 days. A 1M aqueous solution of HCl (20 mL) was added and the crude reaction mixture
10 was extracted 3x with EtOAc (20 mL). The organic layers were combined and washed once with a brine solution (20 mL), dried over Na₂SO₄, and concentrated under vacuum. The crude solid was chromatographed (5-15% EtOAc in hexane) to yield 125 mg (49%) of **93** as an off white solid.

¹H NMR (DMSO-d₆) δ 11.6 (s, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.96 (d, J =
15 2.1 Hz, 1H), 7.88-7.83 (m, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.76-7.73 (m, 1H), 7.1 (dd, J = 8.6, 2.1 Hz, 1H), 7.52-7.44 (m, 3H), 7.32 (s, 2H), 7.21 (s, 2H), 7.1 (dd, J = 8.6, 2.0 Hz, 1H). MS (M-H) 526

EXAMPLE 94

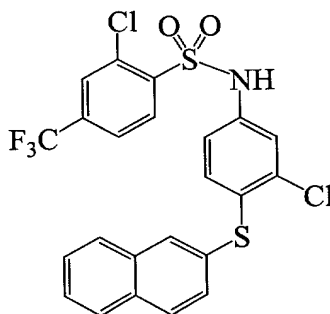


6-Chloro-pyridine-3-sulfonic acid [3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (94).

To a 0.35M solution of 3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90)(150 mg, 0.53 mmol) in THF was added pyridine (Aldrich, 0.21 mL, 2.63 mmol) followed by 6-chloro-pyridine-3-sulfonyl chloride (Qorpark, 122 mg, 0.58 mmol). The resulting mixture was stirred for 15 hours. A 1M aqueous solution of HCl (20 mL) was added and the crude reaction mixture was extracted 3x with EtOAc (50 mL). The organic layers were combined and washed twice with a brine solution (100 mL), dried over Na₂SO₄, and concentrated under vacuum. The crude solid was chromatographed (5-15% EtOAc in hexane) to yield 140 mg (58%) of 94 as a pale yellow solid.

¹H NMR (DMSO-d₆) δ 10.93 (s, 1H), 8.77 (d, J = 2.0 Hz, 1H), 8.19 (dd, J = 8.4, 2.6 Hz, 1H), 7.97-7.90 (m, 2H), 7.90-7.84 (m, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.59-7.52 (m, 2H), 7.36 (dd, J = 8.6, 1.9 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 7.12-7.04 (m, 2H). MS (M-H)

EXAMPLE 95

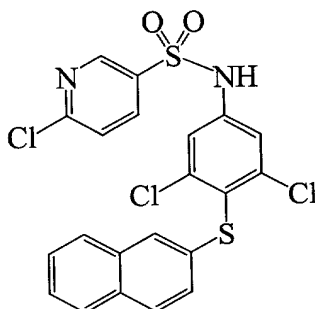


2-Chloro-N-[3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-trifluoromethylbenzenesulfonamide (95)

The title compound was prepared using the method of example 94, starting with 3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (150 mg, 0.53 mmol), pyridine (Aldrich, 0.21 mL, 2.63 mmol) and 2-chloro-4-trifluoromethylbenzenesulfonyl chloride (Maybridge, 162 mg, 0.58 mmol) in THF. 250 mg (90%) of title compound (95) was obtained as a pale yellow solid.

¹H NMR (DMSO-d₆) δ 11.30 (s, 1H), 8.23 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H), 7.97-7.84 (m, 3H), 7.84-7.80 (m, 2H), 7.58-7.50 (m, 2H), 7.32 (dd, J = 8.6, 1.9 Hz, 1H), 7.28 (d, J = 2.3 Hz, 1H), 7.11 (d, J = 8.6 Hz, 1H), 7.04 (dd, J = 8.6, 2.3 Hz, 1H). MS (M-H) 526

EXAMPLE 96

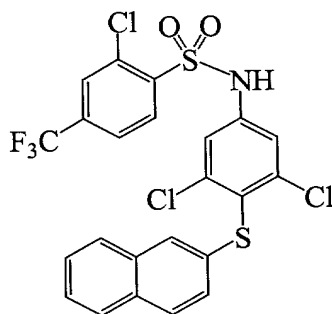


5 **6-Chloro-pyridine-3-sulfonic acid [3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (96)**

The title compound was prepared using the method of example 94, starting with 3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90) (150 mg, 0.47 mmol), pyridine (Aldrich, 0.19 mL, 2.34 mmol) and 6-chloro-pyridine-3-sulfonyl chloride (Qorpark, 109 mg, 0.52 mmol) in THF. 130 mg (56%) of 96 was obtained as a pale yellow solid.

¹H NMR (DMSO-d₆) δ 11.40 (br s, 1H), 8.88 (d, J = 1.9 Hz, 1H), 8.28 (dd, J = 8.4, 1.6 Hz, 1H), 7.88-7.80 (m, 3H), 7.76 (d, J = 9.1, 1.8 Hz, 1H), 7.52-7.42 (m, 3H), 7.38 (s, 2H), 7.14 (dd, J = 8.7, 2.0 Hz, 1H). MS (M-H) 493

15 **EXAMPLE 97**



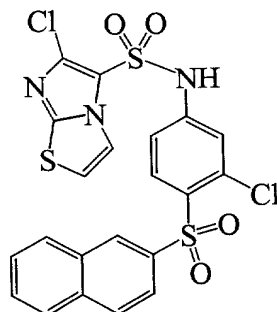
20 **2-Chloro-N-[3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (97)**

The title compound was prepared using the method of example 94, starting with 3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90) (150 mg, 0.47 mmol), pyridine (Aldrich, 0.19 mL, 2.34 mmol) and 2-chloro-4-trifluoromethylbenzenesulfonyl chloride (Maybridge, 144 mg, 0.52 mmol) in THF. 137 mg (52%) of 97 was obtained as a pale yellow solid.

¹H NMR (DMSO-d₆) δ 8.38 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 1.4 Hz, 1H), 8.01 (dd, J = 8.4, 1.1 Hz, 1H), 7.88-7.80 (m, 2H), 7.76-7.71 (m, 1H), 7.51-7.42 (m, 2H), 7.34 (s, 2H), 7.12 (dd, J = 8.6, 2.0 Hz, 1H). MS (M-H) 560

5

EXAMPLE 98

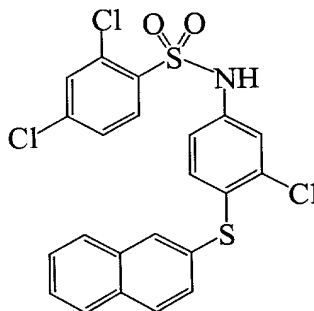


6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid [3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (98)

The title compound was prepared using the method of example 94, starting
10 with 3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (92) (150 mg, 0.53 mmol),
pyridine (Aldrich, 0.21 mL, 2.63 mmol) and 6-chloro-imidazo[2,1-b]thiazole-5-sulfonyl
chloride (Maybridge, 149 mg, 0.58 mmol) in THF. 172 mg (65%) of 98 was obtained as
a pale yellow solid.

¹H NMR (DMSO-d₆) δ 11.26 (s, 1H), 7.98 (d, J = 4.4 Hz, 1H), 7.96-7.88
15 (m, 2H), 7.88-7.84 (m, 2H), 7.68 (d, J = 2.4 Hz, 1H), 7.58-7.52 (m, 2H), 7.33-7.28 (m,
2H), 7.14 (d, J = 8.5 Hz, 1H), 7.01 (dd, J = 8.5, 2.4 Hz, 1H), 7.04 (dd, J = 8.6, 2.3 Hz,
1H). MS (M-H) 504

EXAMPLE 99



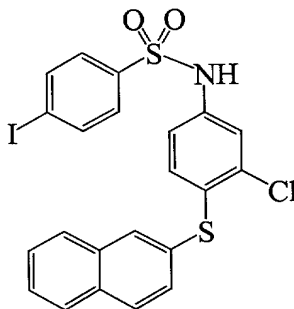
20

2,4-Dichloro-N-[3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-benzene sulfonamide(99)

2,4-Dichloro-N-[3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-benzene sulfonamide was synthesized (67%) from 3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (92) and 2,4-dichlorobenzenesulfonyl chloride, obtained from Maybridge, in a similar manner as described in example 93.

^1H NMR (DMSO- d_6) δ 11.1 (s, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.95-7.88(m, 3H), 7.86-7.81 (m, 2H), 7.65 (dd, J = 8.4 Hz, 1H), 7.57-7.51 (m, 2H), 7.31 (dd, J = 8.6, 1.9 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 8.6, 2.3 Hz, 1H). MS (M-H) 492

EXAMPLE 100

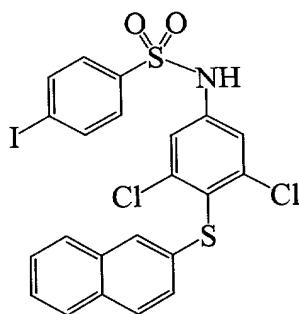


N-[3-Chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-iodobenzenesulfonamide (100)

The title compound was prepared using the method of example 94, starting with 3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (92)(150 mg, 0.53 mmol), pyridine (Aldrich, 0.21 mL, 2.63 mmol) and 4-iodobenzenesulfonyl chloride (Acros, 175 mg, 0.58 mmol) in THF. 153 mg (53%) of 100 was obtained as a pale yellow solid.

^1H NMR (DMSO- d_6) δ 10.75 (s, 1H), 8.01-7.95 (m, 2H), 7.95-7.89 (m, 2H), 7.87-7.82 (m, 2H), 7.59-7.50 (m, 4H), 7.32 (dd, J = 8.6, 1.9 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.04 (dd, J = 8.5, 2.2 Hz, 1H). MS (M-H) 550

EXAMPLE 101

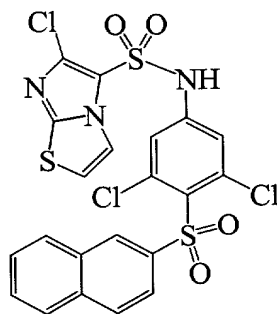


N-[3,5-Dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-iodobenzenesulfonamide(101)

5 The title compound was prepared using the method of example 94, starting with 3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90) (150 mg, 0.47 mmol), pyridine (Aldrich, 0.19 mL, 2.34 mmol) and 4-iodobenzenesulfonyl chloride (Acros, 155 mg, 0.52 mmol) in THF. 254 mg (93%) of 101 was obtained as a pale yellow solid.

¹H NMR (DMSO-d₆) δ 11.22 (s, 1H), 8.08-8.02 (m, 2H), 7.88-7.82 (m, 2H), 7.74 (d, J = 7.7 Hz, 1H), 7.65-7.58 (m, 2H), 7.52-7.40 (m, 3H), 7.35 (s, 2H), 7.12 (dd, J = 8.7, 1.9 Hz, 1H). MS (M-H) 584

EXAMPLE 102



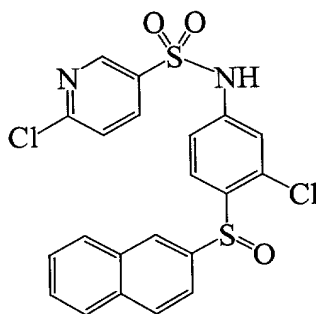
6-Chloro-imidazo[2,1-*b*]thiazole-5-sulfonic acid [3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (102)

15 The title compound was prepared using the method of example 94, starting with 3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90)(150 mg, 0.47 mmol), pyridine (Aldrich, 0.19 mL, 2.34 mmol) and 6-chloro-imidazo[2,1-*b*]thiazole-5-sulfonyl chloride (Maybridge, 132 mg, 0.52 mmol) in THF. 172 mg (65%) of 102 was obtained as a pale yellow solid.

^1H NMR (DMSO- d_6) δ 11.71 (br s, 1H), 8.02 (d, J = 4.4 Hz, 1H), 7.89-7.82 (m, 2H), 7.77 (m, 1H), 7.72 (d, J = 4.4 Hz, 1H), 7.52-7.432 (m, 3H), 7.35 (s, 2H), 7.11 (dd, J = 8.7, 2.0 Hz, 1H). MS (M-H) 504

5

EXAMPLE 103

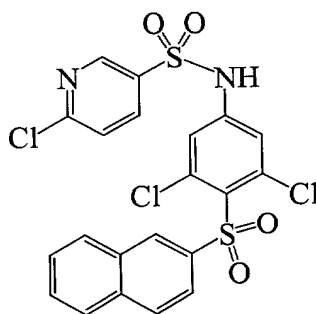


6-Chloro-pyridine-3-sulfonyl [3-chloro-4-(naphthalene-2-sulfonyl)-phenyl]-amide (103)

To a solution of 6-Chloro-pyridine-3-sulfonyl [3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (**94**, 55 mg, 0.12 mmol) in CH_2Cl_2 (2 mL), was added dropwise a solution of *m*-chloroperoxybenzoic acid (mCPBA, Aldrich, 36mg, 0.12 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at ambient temperature for 1 hour and diluted with EtOAc (60 mL). The organic layer was washed with saturated aqueous NaHCO_3 solution (50 mL), twice with brine solution (50 mL), dried over Na_2SO_4 , and concentrated under vacuum. The crude solid was chromatographed (10-25% EtOAc in hexane) to yield 17 mg (30%) of **103** as an off white solid.

^1H NMR (DMSO- d_6) δ 11.25 (s, 1H), 8.82 (d, J = 2.6 Hz, 1H), 8.43 (d, J = 1.5 Hz, 1H), 8.19 (dd, J = 8.4, 2.6 Hz, 1H), 8.10 (m, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.98 (m, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.70-7.60 (m, 2H), 7.53 (dd, J = 8.7, 1.8 Hz, 1H), 7.40 (dd, J = 8.5, 2.2 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H). MS (M-H) 475

EXAMPLE 104

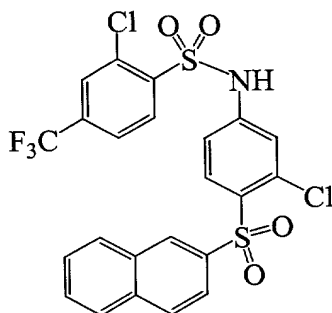


6-Chloro-pyridine-3-sulfonic acid [3,5-dichloro-4-(naphthalene-2-sulfonyl)-phenyl]-amide (104)

5 To a solution of 6-Chloro-pyridine-3-sulfonic acid [3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (**96**, 20 mg, 0.04 mmol) in CH_2Cl_2 (1 mL), was added dropwise a solution of mCPBA (Aldrich, 36 mg, 0.12 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at ambient temperature overnight and diluted with EtOAc (60 mL). The organic layer was washed twice with 5% aqueous $\text{Na}_2\text{S}_2\text{O}_3$
10 solution (20 mL), twice with 1% aqueous NaHCO_3 solution (20 mL), and brine solution (20 mL), dried over Na_2SO_4 . Removal of the solvent under vacuum gave 21 mg (99%) of **104** as an off white solid.

^1H NMR ($\text{DMSO}-d_6$) δ 8.68 (d, $J = 2.5$ Hz, 1H), 8.58 (d, $J = 1.8$ Hz, 1H), 8.22 (d, $J = 8.1$ Hz, 1H), 8.12-8.05 (m, 2H), 8.02 (d, $J = 8.0$ Hz, 1H), 7.79 (dd, $J = 8.7, 2.0$
15 Hz, 1H), 7.76-7.64 (m, 2H), 7.58 (d, $J = 8.4$ Hz, 1H), 6.93 (s, 2H). MS (M-H) 525

EXAMPLE 105



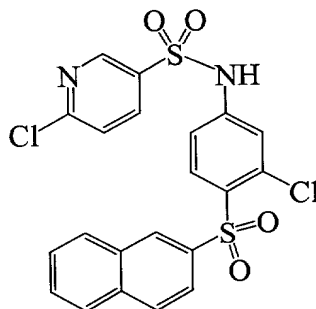
2-Chloro-N-[3-chloro-4-(naphthalene-2-sulfonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (105)

20 The title compound was prepared using the method of example 104, starting with 2-Chloro-N-[3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-

trifluoromethylbenzene-sulfonamide (95, 35 mg, 0.066 mmol), *m*CPBA (Aldrich, 100 mg, 0.33 mmol) in CH₂Cl₂. 38 mg (100%) of 105 was obtained as an off white solid.

¹H NMR (DMSO-d₆) δ 11.90 (br s, 1H), 8.62 (d, J = 1.8 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 8.16-8.00 (m, 4H), 7.90 (d, J = 8.5 Hz, 1H), 7.77-7.64 (m, 3H), 7.20 (d, J = 9.0 Hz, 1H), 7.09 (s, 1H). MS (M-H) 558

EXAMPLE 106



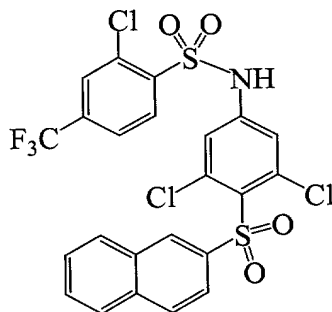
10 6-Chloro-pyridine-3-sulfonic acid [3-chloro-4-(naphthalene-2-sulfonyl)-phenyl]-amide (106)

The title compound was prepared using the method of example 104, starting with 6-Chloro-pyridine-3-sulfonic acid [3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (94, 15 mg, 0.03 mmol), *m*CPBA (Aldrich, 50 mg, 0.15 mmol) in CH₂Cl₂. 16 mg (100%) of 106 was obtained as an off white solid.

15 ¹H NMR (DMSO-d₆) δ 11.60 (br s, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.62 (d, J = 1.8 Hz, 1H), 8.24-8.16 (m, 2H), 8.14 (d, J = 8.8 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.76-7.64 (m, 4H), 7.27 (dd, J = 8.8, 2.0 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H). MS (M-H) 491

20

EXAMPLE 107



2-Chloro-N-[3,5-dichloro-4-(naphthalene-2-sulfonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (107)

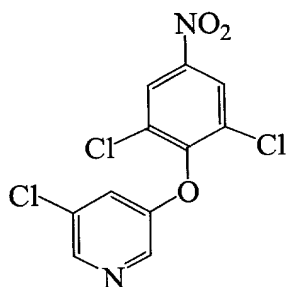
The title compound was prepared using the method of example 104, starting with 2-Chloro-N-[3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-trifluoromethylbenzene-sulfonamide (97, 30 mg, 0.05 mmol), *m*CPBA (Aldrich, 80 mg, 0.26 mmol) in CH₂Cl₂. 32 mg (100%) of 107 was obtained as an off white solid.

¹H NMR (DMSO-*d*₆) δ 8.59 (d, *J* = 1.1 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.90 (s, 1H), 7.84-7.77 (m, 2H), 7.75-7.64 (m, 2H), 6.92 (s, 2H). MS (M-H) 592

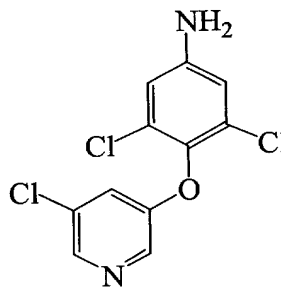
10

EXAMPLE 108

This example illustrates the preparation of 108.1 through 108.6.



108.1



108.2

A solution of potassium *t*-butoxide (1 M in THF; 26.5 mL) was added to a solution of 3,4,5-trichloronitrobenzene (3 g) and 5-chloro-3-hydroxypyridine (1.7 g) in THF (15 mL). The deep red solution was heated at 50°C overnight, then poured into water. The precipitate was collected by filtration and purified by chromatography on silica (10% ethyl acetate/hexanes as eluant) to provide 108.1.

¹H NMR (400 MHz) (DMSO-*d*₆) δ 8.58 (s, 2H); 8.47 (d, *J*=2 Hz, 1H); 8.41 (d, *J*=2.6 Hz, 1H); 7.72 (dd, *J*=2.6, 2 Hz, 1H).

20

Using the method of Example 2, 108.1 (2.2 g) was converted to the aniline

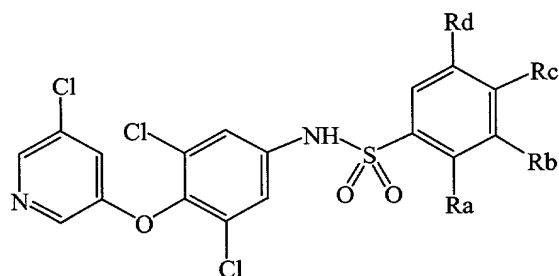
108.2.

¹H NMR (400 MHz) (DMSO-*d*₆) δ 8.35 (d, *J*=2 Hz, 1H); 8.21 (d, *J*=2.5 Hz, 1H); 7.37 (dd, *J*=2.5, 2 Hz, 1H); 6.73 (s, 2H); 5.78 (br s, 2H).

The compounds provided in Table 17 were prepared using **108.2** and commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

5

Table 17

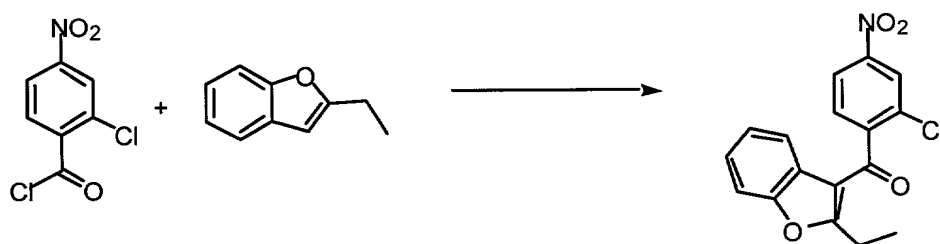


	Ra	Rb	Rc	Rd	mp (°C)
108.3	H	Cl	Cl	H	199-200
108.4	Cl	H	Cl	H	166-169
108.5	H	H	I	H	211-214
108.6	Cl	H	CF ₃	H	185-189

EXAMPLE 109

This example illustrates the synthesis of **109.1**.

10



109.1

A round-bottomed flask was charged with 2-chloro-4-nitrobenzoyl chloride (3.50 g, 15.9 mmol), 2-ethylbenzofuran (2.11 g, 14.4 mmol), and anhydrous methylene chloride (20 mL). This was cooled in an ice/water bath and titanium tetrachloride (5.49 g, 28.9 mmol) was added in a dropwise fashion with vigorous stirring. After addition was complete, the reaction was stirred at 0°C for 20 minutes and then was warmed to room temperature for an additional four hours. The reaction was then diluted with 80 mL of methylene chloride and washed twice with 50 mL volumes of 2N HCl and then once with 50 mL of brine. The organics were dried over Na₂SO₄ and concentrated to

15

20

a yellow oil. This oil was further purified using silica gel flash chromatography (eluting with 20% hexanes in methylene chloride). The desired fractions were concentrated to give 2.9 g (61%) of ketone **109.1** as an off-white solid.

MS ESI m/e: 330.0 (M + H).

5

EXAMPLE 110

(2,6-Dichloro-4-nitro-phenyl)-acetic acid (110)

To a solution of diethyl malonate (Aldrich, 13.8 mL, 90 mmol) in DMF (60 mL) was added cesium carbonate (Aldrich, 48.9 g, 150 mmol). The mixture was
10 heated to 70 °C and then was added 1,2,3-trichloro-5-nitrobenzene (Aldrich, 13.56 g, 60 mmol). The mixture was stirred at 70°C for 3 hours and cooled to room temperature. A 2M aqueous solution of HCl (50 mL) was added and the crude reaction mixture was extracted 3x with EtOAc (150 mL). The organic layers were combined and washed twice with a brine solution (150 mL), dried over Na₂SO₄, and concentrated under vacuum. The
15 light yellow oil was used for the next reaction without further purification.

The light yellow oil was suspended in 90 mL of 6 N aqueous HCl. The mixture was refluxed overnight (15 hours). The mixture was cooled in the ice bath for 2 hours and filtered. The crude solid product was triturated with CH₂Cl₂/Hexanes to give compound 110 (11.5 g, 77%) as pale brown solid.

20 ¹H NMR (DMSO-d₆) δ 13.00 (br s, 1H), 8.23 (s, 2H), 4.16 (s, 2H).

EXAMPLE 111

(2-Chloro-4-nitro-phenyl)-acetic acid (111)

The title compound was prepared using the method of example 110,
25 starting with diethyl malonate (Aldrich, 30.5 mL, 200 mmol), 3,4-dichloronitrobenzene (Aldrich, 19.2 g, 100 mmol), cesium carbonate (Aldrich, 81.5 g, 250 mmol) and 150 mL of aqueous 6N HCl solution. 18.8 g (87%) of compound 111 was obtained as pale yellow solid.

¹H NMR (DMSO-d₆) δ 12.80 (br s, 1H), 8.29 (d, J = 2.4 Hz, 1H), 8.18
30 (dd, J = 8.4, 2.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 3.90 (s, 2H).

EXAMPLE 112

2-Amino-4-chloro-benzenethiol hydrochloride (112)

By the procedure of R.L.Danley and D. A. Zazaris (Can. J. Chem. 43, 2610-2612 (1965)) sodium tetrasulfide was obtained by dissolving sulfur (Aldrich, 9.6 g, 300 mmol) in molten sodium sulfide nonahydrate (Aldrich, 24.0 g, 100 mmol). This hot liquid was added to a solution of 2,5-dichloronitrobenzene (Aldrich, 38.4 g, 200 mmol) in 95% ethanol (140 mL). After the exothermic reaction had ceased, the mixture was refluxed for 2 hours and filtered while hot. The precipitate was washed with water (50 mL) and ethanol (50 mL) to give 37.7 g of intermediate trisulfide as a yellow solid.

^1H NMR (CDCl_3) δ 8.83 (d, $J = 2.3$ Hz, 1H), 7.76 (d, $J = 8.6$ Hz, 1H), 7.55 (dd, $J = 8.6, 2.3$ Hz, 1H).

Concentrated hydrochloric acid (125 mL) was slowly (overnight, 15 hours) added to a well-stirred suspension of the trisulfide (37.7 g) described above and tin (Aldrich, 88 g, 737 mmol) in 95% ethanol (200 mL). After filtration of the hot solution, the filtrate was allowed to stand at room temperature overnight to precipitate the crude product. The precipitate was collected by filtration, washed with 1:1 ethanol/concentrated HCl. Recrystallization from 1:1 MeOH/concentrated HCl gave compound 112 (13.8 g) as white needles.

^1H NMR ($\text{DMSO}-d_6$) δ 6.96 (d, $J = 8.3$ Hz, 1H), 6.86 (d, $J = 2.3$ Hz, 1H), 6.50 (dd, $J = 8.3, 2.3$ Hz, 1H).

EXAMPLE 113

2-Amino-4-methyl-benzenethiol hydrochloride (113)

bis-(4-Methyl-2-nitrophenyl)-trisulfide was prepared using the method in example 112, starting from 4-chloro-3-nitro-toluene (Aldrich, 34.3 g, 200 mmol), sulfur (Aldrich, 9.6 g, 300 mmol) and sodium sulfide nonahydrate (Aldrich, 24.0 g, 100 mmol) in 95% EtOH (150 mL). 27.7 g of the trisulfide was obtained as a yellow solid.

^1H NMR (400MHz, CDCl_3) δ 8.21 (d, $J = 8.3$ Hz, 1H), 8.07 (br s, 1H), 7.58 (dd, $J = 8.3, 1.3$ Hz, 1H), 2.48 (s, 3H).

Reduction of the *bis*-(4-Methyl-2-nitrophenyl)trisulfide as in example 112 gave compound 113 (11.3 g) as a mixture after recrystallization, but which was used directly in subsequent reactions.

EXAMPLE 114

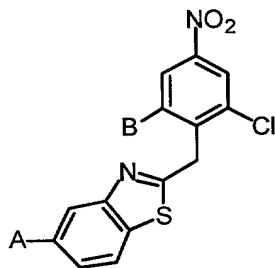
5-Chloro-2-(2,6-dichloro-4-nitro-benzyl)-benzothiazole (114)

By a modification of the procedure of D.L. Boger (J. Org. Chem. 43, 2296-2297 (1978)) a solution of $P_2O_5/MeSO_3H$ (Aldrich, 7.5 g, 1:10, w:w) was treated with 2-amino-4-chloro-benzenethiol hydrochloride (example 112, 1.96 g, 10.0 mmol) and (2,6-dichloro-4-nitro-phenyl)-acetic acid (example 110, 2.50 g, 10.0 mmol). The resulting mixture was stirred at room temperature for 1 hour, then heated at 90°C overnight (15 hours). After cooled to room temperature, the reaction mixture was poured to ice and the resulting mixture was extracted 3x with EtOAc (50 mL). The organic layers were combined and washed twice with a brine solution (100 mL), dried over Na_2SO_4 , and concentrated under vacuum. The crude solid was chromatographed (CH_2Cl_2) to yield 3.7 g (99%) of compound 114 as a pale yellow solid.

1H NMR ($CDCl_3$) δ 8.28 (s, 2H), 7.98 (d, $J = 1.9$ Hz, 1H), 7.76 (d, $J = 8.5$ Hz, 1H), 7.38 (dd, $J = 8.5, 1.9$ Hz, 1H), 4.87 (s, 2H). MS (M+H) 373

The compounds of Table 18 were prepared using the method of example 114.

Table 18



	Example	A	B	yield
20	114	Cl	Cl	99%
	115	Cl	H	98%
	116	CF ₃	Cl	96%
	117	CF ₃	H	89%
	118	H	Cl	92%
25	119	H	H	77%
	120	Me	Cl	20%
	121	Me	H	28%

EXAMPLE 115

5-Chloro-2-(2-chloro-4-nitro-benzyl)-benzothiazole

¹H NMR (400MHz, DMSO-d₆) δ 8.35 (d, J = 2.3 Hz, 1H), 8.25 (dd, J = 8.5, 2.4 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.48 (dd, J = 8.6, 2.0 Hz, 1H), 4.77 (s, 2H). MS (M+H) 339

EXAMPLE 116

2-(2,6-Dichloro-4-nitro-benzyl)-5-trifluoromethyl-benzothiazole

¹H NMR (DMSO-d₆) δ 8.42 (s, 2H), 8.34 (d, J = 8.4 Hz, 1H), 8.28 (br s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 4.94 (s, 2H). MS (M+H) 407

EXAMPLE 117

2-(2-Chloro-4-nitro-benzyl)-5-trifluoromethyl-benzothiazole

¹H NMR (CDCl₃) δ 8.33 (d, J = 2.3 Hz, 1H), 8.27 (br s, 1H), 8.14 (dd, J = 8.5, 2.3 Hz, 1H), 7.96 (br d, J = 8.3 Hz, 1H), 7.63 (d, J = 8.5 Hz, 2H) 4.70 (s, 2H). MS (M+H) 371

EXAMPLE 118

2-(2,6-Dichloro-4-nitro-benzyl)-benzothiazole

¹H NMR (DMSO-d₆) δ 8.41 (s, 2H), 8.06 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.50-7.38 (m, 2H), 4.94 (s, 2H). MS (M-H) 337

EXAMPLE 119

2-(2-Chloro-4-nitro-benzyl)-benzothiazole

¹H NMR (CDCl₃) δ 8.35 (d, J = 2.2 Hz, 1H), 8.25 (dd, J = 8.4, 2.2 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 4.76 (s, 2H). MS (M+H) 305

EXAMPLE 120

2-(2,6-Dichloro-4-nitro-benzyl)-5-methyl-benzothiazole

¹H NMR (DMSO-d₆) δ 8.41 (s, 2H), 7.91 (d, J = 8.2 Hz, 1H), 7.71 (br s, 1H), 7.25 (d, J = 8.2 Hz, 1H), 4.85 (s, 2H), 2.41 (s, 3H). MS (M+H) 353 .

EXAMPLE 121

2-(2-Chloro-4-nitro-benzyl)-5-methyl-benzothiazole

¹H NMR (DMSO-d₆) δ 8.35 (d, J = 2.3 Hz, 1H), 8.24 (dd, J = 8.5, 2.3 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.74 (br s, 1H), 7.25 (dd, J = 8.2, 1.0 Hz, 1H), 4.73 (s, 2H), 2.42 (s, 3H). MS (M-H) 317

Reduction of the compounds of Table 18 gave the anilines of Table 19.

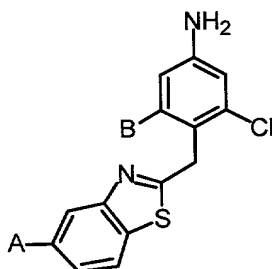


Table 19

Example	A	B	Method	yield
10 122	Cl	Cl	A	100%
123	Cl	H	B	88%
124	CF ₃	Cl	A	90%
125	CF ₃	H	B	89%
126	H	Cl	B	97%
15 127	H	H	B	90%
128	Me	Cl	B	97%
129	Me	H	B	97%

Method A: see example 90

Method B: see example 181

EXAMPLE 122

3,5-Dichloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenylamine

¹H NMR (DMSO-d₆) δ 8.03 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.45 (dd, J = 8.5, 2.2 Hz, 1H), 6.70 (s, 2H), 5.79 (s, 2H), 4.52 (s, 2H). MS (M+H) 343

EXAMPLE 123

3-Chloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenylamine

¹H NMR (DMSO-d₆) δ 8.05-7.95 (m, 2H), 7.43 (dd, J = 8.5, 2.1 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.66 (d, J = 2.2 Hz, 1H), 6.53 (dd, J = 8.2, 2.2 Hz, 1H), 5.44 (s, 2H), 4.36 (s, 2H). MS (M+H) 309.

EXAMPLE 124

3,5-Dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenylamine

5 ^1H NMR (DMSO- d_6) δ 8.29 (br s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4Hz, 1H), 6.70 (s, 2H), 5.81(s, 2H), 4.56 (s, 2H). MS (M+H) 377

EXAMPLE 125

3-Chloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenylamine

10 ^1H NMR (DMSO- d_6) δ 8.25 (br s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.72 (dd, J = 8.4, 1.3 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 2.2 Hz, 1H), 6.54 (dd, J = 8.2, 2.2 Hz, 1H), 5.46 (s, 2H), 4.40 (s, 2H). MS (M+H) 343

EXAMPLE 126

4-Benzothiazol-2-ylmethyl-3,5-dichloro-phenylamine

15 ^1H NMR (DMSO- d_6) δ 7.99 (dd, J = 8.0, 0.6 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.45 (td, J = 8.2, 1.2 Hz, 1H), 7.38 (td, J = 8.0, 1.0 Hz, 1H), 6.70 (s, 2H), 5.78(s, 2H), 4.51 (s, 2H). MS (M+H) 309.

EXAMPLE 127

4-Benzothiazol-2-ylmethyl-3-chloro-phenylamine

20 ^1H NMR (DMSO- d_6) δ 7.98 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.47 (td, J = 7.9, 1.2 Hz, 1H), 7.38 (td, J = 7.9, 1.0 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.66 (d, J = 2.2 Hz, 1H), 6.54 (dd, J = 8.2, 2.2 Hz, 1H), 5.44 (s, 2H), 4.35 (s, 2H). MS (M+H)
25 275

EXAMPLE 128

3,5-Dichloro-4-(5-methyl-benzothiazol-2-ylmethyl)-phenylamine

30 ^1H NMR (DMSO- d_6) δ 7.84 (d, J = 8.2 Hz, 1H), 7.73 (br s, 1H), 7.21 (dd, J = 8.2, 1.0 Hz, 1H), 6.69 (s, 2H), 5.77 (s, 2H), 4.48 (s, 2H), 2.43 (s, 3H). MS (M+H) 323.

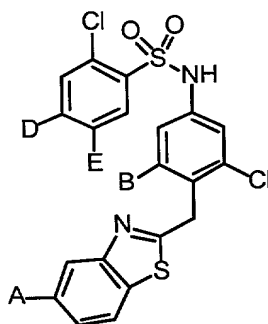
EXAMPLE 129

3-Chloro-4-(5-methyl-benzothiazol-2-ylmethyl)-phenylamine

^1H NMR (DMSO- d_6) δ 7.84 (d, J = 8.2 Hz, 1H), 7.73 (s, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 2.1 Hz, 1H), 6.52 (dd, J = 8.2, 2.1 Hz, 1H), 5.41 (s, 2H), 4.32 (s, 2H), 2.43 (s, 3H). MS (M+H) 289.

The compounds of **Table 20** were prepared using the method of example 94 from compounds in **Table 19** and corresponding arylsulfonyl chloride.

Table 20



Example	A	B	D	E	yield
10 130	Cl	Cl	CF ₃	H	83%
131	Cl	Cl	Cl	H	63%
132	Cl	Cl	Cl	Me	73%
15 133	Cl	H	CF ₃	H	78%
134	CF ₃	Cl	CF ₃	H	74%
135	CF ₃	Cl	Cl	H	82%
136	CF ₃	H	CF ₃	H	55%
137	CF ₃	H	Cl	H	26%
20 138	H	Cl	CF ₃	H	67%
139	H	Cl	Cl	H	55%
140	H	Cl	Cl	Me	85%
141	H	H	CF ₃	H	64%
142	Me	Cl	CF ₃	H	84%
25 143	Me	H	CF ₃	H	88%

EXAMPLE 130

2-Chloro-N-[3,5-dichloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

¹H NMR (DMSO-d₆) δ 11.56 (br s, 1H), 8.35 (d, J = 8.2 Hz, 1H), 8.20 (d, J = 1.1 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 8.00-7.95 (m, 2H), 7.45 (dd, J = 8.6, 2.1 Hz, 1H), 7.23 (s, 2H), 4.62 (s, 2H). MS (M-H) 583

EXAMPLE 131

2,4-Dichloro-N-[3,5-dichloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenyl]-benzenesulfonamide

¹H NMR (DMSO-d₆) δ 11.40 (br s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.70 (dd, J = 8.6, 2.1 Hz, 1H), 7.46 (dd, J = 8.6, 2.0 Hz, 1H), 7.20 (s, 2H), 4.62 (s, 2H). MS (M-H) 549

EXAMPLE 132

2,4-Dichloro-N-[3,5-dichloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenyl]-5-methyl-benzenesulfonamide

¹H NMR (DMSO-d₆) δ 11.33 (br s, 1H), 8.28 (s, 1H), 8.17 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 8.01 (d, J = 1.9 Hz, 1H), 7.87 (s, 1H), 7.45 (dd, J = 8.6, 1.9 Hz, 1H), 7.22 (s, 2H), 4.61 (s, 2H), 2.40 (s, 3H). MS (M-H) 563

EXAMPLE 133

2-Chloro-N-[3-chloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

¹H NMR (DMSO-d₆) δ 11.24 (br s, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.16 (br s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 1.8 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 8.4, 2.0 Hz, 1H), 4.47 (s, 2H). MS (M-H)⁺ 549

EXAMPLE 134

2-Chloro-*N*-[3,5-dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

¹H NMR (DMSO-d₆) δ 11.56 (s, 1H), 8.35 (d, J = 8.2 Hz, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.26 (br s, 1H), 8.20 (br s, 1H), 7.99 (dd, J = 8.3, 1.0 Hz, 1H), 7.73 (dd, J = 8.2, 1.2 Hz, 1H), 7.24 (s, 2H), 4.67 (s, 2H). MS (M-H) 617

EXAMPLE 135

2,4-Dichloro-*N*-[3,5-dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenyl]-benzenesulfonamide

¹H NMR (DMSO-d₆) δ 11.41 (s, 1H), 8.29 (br s, 1H), 8.27 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.73 (dd, J = 8.4, 1.4 Hz, 1H), 7.70 (dd, J = 8.6, 2.0 Hz, 1H), 7.21 (s, 2H), 4.67 (s, 2H). MS (M-H)

EXAMPLE 136

2-Chloro-*N*-[3-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

¹H NMR (DMSO-d₆) δ 11.25 (br s, 1H), 8.32-8.22 (m, 3H), 8.16 (br s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.21 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 4.52 (s, 2H). MS (M-H) 583

EXAMPLE 137

2,4-Dichloro-*N*-[3-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenyl]-benzenesulfonamide

¹H NMR (DMSO-d₆) δ 11.10 (br s, 1H), 8.28 (br s, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.4, 1.4 Hz, 1H), 7.65 (dd, J = 8.6, 2.1 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 7.10 (dd, J = 8.3, 2.2 Hz, 1H), 4.52 (s, 2H). MS (M-H) 549

EXAMPLE 138

***N*-(4-Benzothiazol-2-ylmethyl-3,5-dichloro-phenyl)-2-chloro-4-trifluoromethyl-benzenesulfonamide**

¹H NMR (DMSO-d₆) δ 11.54 (s, 1H), 8.35 (d, J = 8.3 Hz, 1H), 8.20 (br s, 1H), 7.99 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 7.8 Hz, 1H), 7.46 (td, J = 8.0, 1.0 Hz, 1H), 7.40 (td, J = 7.8, 0.9 Hz, 1H), 7.23 (s, 2H), 4.61 (s, 2H). MS (M-H) 549

EXAMPLE 139

***N*-(4-Benzothiazol-2-ylmethyl-3,5-dichloro-phenyl)-2,4-dichloro-benzenesulfonamide**

¹H NMR (DMSO-d₆) δ 11.38 (s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.70 (dd, J = 8.6, 2.0 Hz, 1H), 7.46 (m, 1H), 7.40 (m, 1H), 7.20 (s, 2H), 4.60 (s, 2H). MS (M-H) 515

EXAMPLE 140

***N*-(4-Benzothiazol-2-ylmethyl-3,5-dichloro-phenyl)-2,4-dichloro-5-methyl-benzenesulfonamide**

¹H NMR (DMSO-d₆) δ 11.32 (s, 1H), 8.17 (s, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.88 (s, 1H), 7.46 (t, J = 7.3 Hz, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.16 (s, 2H), 4.60 (s, 2H), 2.40 (s, 3H). MS (M-H) 531

EXAMPLE 141

***N*-(4-Benzothiazol-2-ylmethyl-3-chloro-phenyl)-2-chloro-4-trifluoromethyl-benzenesulfonamide**

¹H NMR (DMSO-d₆) δ 11.23 (br s, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.15 (br s, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.46 (td, J = 7.9, 1.0 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.20 (d, J = 2.1 Hz, 1H), 7.11 (dd, J = 8.3, 2.1 Hz, 1H), 4.46 (s, 2H). MS (M-H) 517

EXAMPLE 142

2-Chloro-*N*-[3,5-dichloro-4-(5-methyl-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

¹H NMR (DMSO-*d*₆) δ 11.54 (s, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 8.19 (br s, 1H), 8.00 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.70 (br s, 1H), 7.26-7.18 (m, 3H), 4.58 (s, 2H), 2.40 (s, 3H). MS (M-H) 563

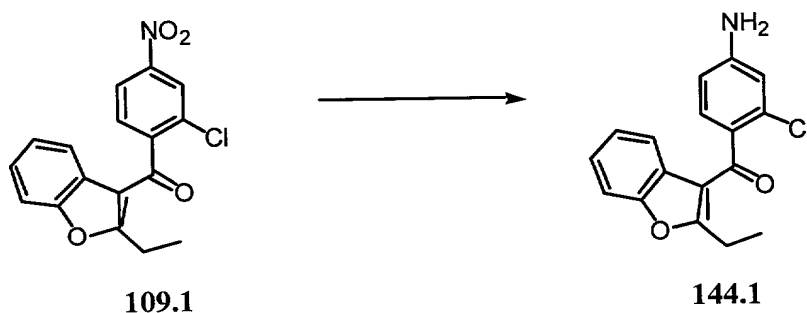
EXAMPLE 143

2-Chloro-*N*-[3-chloro-4-(5-methyl-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

¹H NMR (DMSO-*d*₆) δ 11.22 (br s, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 8.15 (br s, 1H), 7.45 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.71 (br s, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.24-7.19 (m, 2H), 7.05 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.43 (s, 2H), 2.41 (s, 3H). MS (M-H) 529

EXAMPLE 144

This example illustrates the synthesis of 144.1.



20

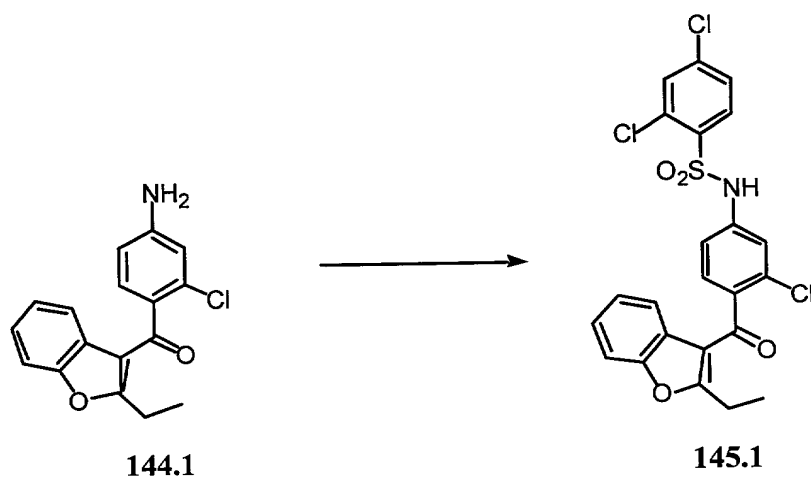
Nitro compound 109.1 (1.91 g, 5.8 mmol) was reduced to the corresponding aniline using SnCl₂•2H₂O (6.54 g, 29.0 mmol) in EtOAc (40 mL) according to the procedure previously described in Example 30. This yielded 692 mg (40%) of compound 144.1 as a white powder.

25

MS ESI *m/e*: 300.0 (M + H).

EXAMPLE 145

This example illustrates the synthesis of 145.1.

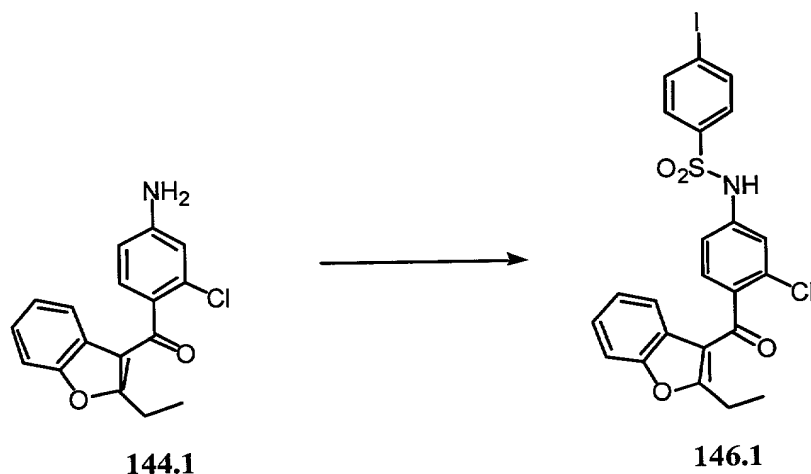


A round-bottomed flask was charged with aniline **144.1** (110 mg, 0.37
 5 mmol), 2,4-dichlorobenzenesulfonyl chloride (108 mg, 0.44 mmol), 2,6-lutidine (47 mg,
 0.44 mmol), catalytic DMAP, and methylene chloride (2.0 mL). The reaction was
 allowed to stir overnight. The reaction was then diluted with 20 mL of methylene
 chloride and washed with 10 mL of 1N HCl and 10 mL of brine. The organics were dried
 over Na₂SO₄ and concentrated to a yellow oil. This oil was further purified using silica
 10 gel flash chromatography. The desired fractions were combined and concentrated to
 yield 60 mg (32%) of compound **145.1** as a white foam.

¹H NMR (400MHz) (*d*₆-DMSO) δ 11.36 (1H, s); 8.12 (1H, d, *J*=8.6 Hz);
 7.94 (1H, d, *J*=2.1 Hz); 7.68 (1H, dd, *J*=8.6, 2.1 Hz); 8.63 (1H, d, *J*=8.4 Hz); 7.47 (1H, d,
J=8.4 Hz); 7.36-7.32 (1H, m); 7.27-7.19 (4H, m); 2.54 (2H, q, *J*= 7.6 Hz); 1.08 (3H, t,
 15 *J*=7.6 Hz). MS ESI *m/e*: 506.0 (M - H).

EXAMPLE 146

This example illustrates the synthesis of **146.1**.

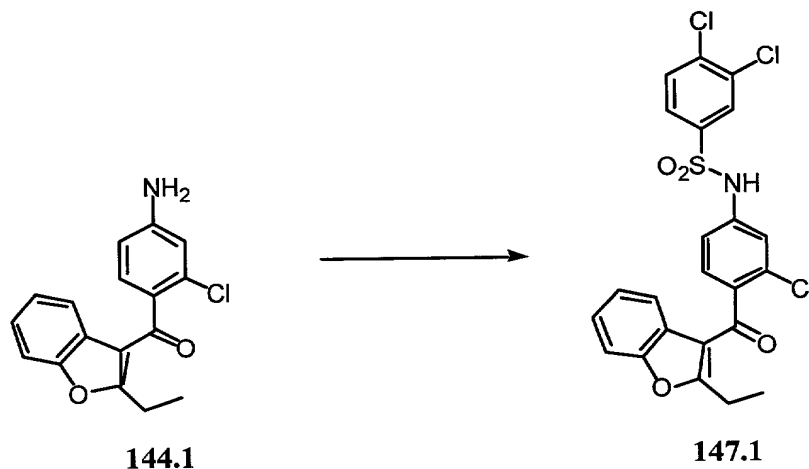


5 Aniline **144.1** (111 mg, 0.37 mmol), p-toluenesulfonyl chloride (135 mg, 0.45 mmol), 2,6-lutidine (48 mg, 0.45 mmol), and catalytic DMAP were combined in methylene chloride (2.0 mL) according to the procedure described in Example 77. This yielded 140 mg (67%) of compound **146.1** as a white foam.

¹H NMR (400MHz) (*d*₆-DMSO) δ 10.97 (1H, s); 8.01 (2H, d, *J*=8.4 Hz); 7.63 (1H, d, *J*=8.4 Hz); 7.58 (2H, d, *J*=8.4 Hz); 7.46 (1H, d, *J*=8.4 Hz); 7.34 (1H, m);
 10 7.46-7.20 (4H, m); 2.54 (2H, q, *J*=7.5 Hz); 1.09 (3H, t, *J*=7.5 Hz). MS ESI *m/e*: 563.9 (M - H).

EXAMPLE 147

This example illustrates the synthesis of **147.1**.



15

Aniline **144.1** (108 mg, 0.36 mmol), 3,4-dichlorobenzenesulfonyl chloride (106 mg, 0.43 mmol), 2,6-lutidine (46 mg, 0.43 mmol), and catalytic DMAP were

combined in methylene chloride (2.0 mL) according to the procedure described in Example 77. This yielded 113 mg (62%) of compound **147.1** as a white foam.

¹H NMR (400MHz) (CDCl₃) δ 7.96 (1H, d, *J*=2.2 Hz); 7.66 (1H, dd, *J*=8.4, 2.2 Hz); 7.57 (1H, d, *J*=8.4 Hz); 7.46 (1H, d, *J*=8.3 Hz); 7.34 (1H, d, *J*=8.3 Hz); 7.31-7.26 (3H, m); 7.20-7.15 (2H, m); 2.79 (2H, q, *J*=7.6 Hz); 1.27 (3H, t, *J*=7.6 Hz).
MS ESI *m/e*: 506.0 (M - H).

EXAMPLE 148

This illustrates the synthesis of (2-fluoro-4-nitro-phenyl)acetic acid **148**.

A round-bottomed flask was charged with diethyl malonate (8.6 g, 54 mmol), cesium carbonate (29.3 g, 90 mmol), and anhydrous DMF (36 mL). The mixture was warmed to 70 °C and 2,4-difluoronitrobenzene (5.75 g, 36 mmol) was added in a dropwise fashion with vigorous stirring. The reaction medium immediately turned dark purple. After the addition was complete, the reaction was stirred at 70°C for 30 minutes. After cooling to room temperature, the reaction was quenched with 4 mL of acetic acid and then poured into 300 mL of 0.3 N HCl_(aq). The purple color discharged completely upon addition to the acid. The mixture was then neutralized by adding solid NaHCO₃ until no gas evolution took place. The mixture was extracted 2 x 150 mL 1:1 diethyl ether:hexanes. The combined organic layers were washed 2 x 100 mL DI water and 1 x 50 mL sat. brine. The organic layer was dried over MgSO₄ and concentrated to a yellow oil. This oil was suspended in 40 mL of 6N HCl_(aq) and the mixture heated to reflux for 16 h. Upon cooling, crystals separated and were collected by filtration. The crystals were dried under vacuum to yield 2-fluoro-4-nitro-phenylacetic acid (**148**) as off-white crystals (5.42 g).

¹H NMR (400MHz) (*d*₄-MeOH) δ 8.06 (1H, d); 8.04 (1H, d); 7.60 (1H, t); 3.81 (2H, s).

EXAMPLE 149

This illustrates the synthesis of 7-chloro-2-(2-fluoro-4-nitro-benzyl)-benzoxazole **149**.

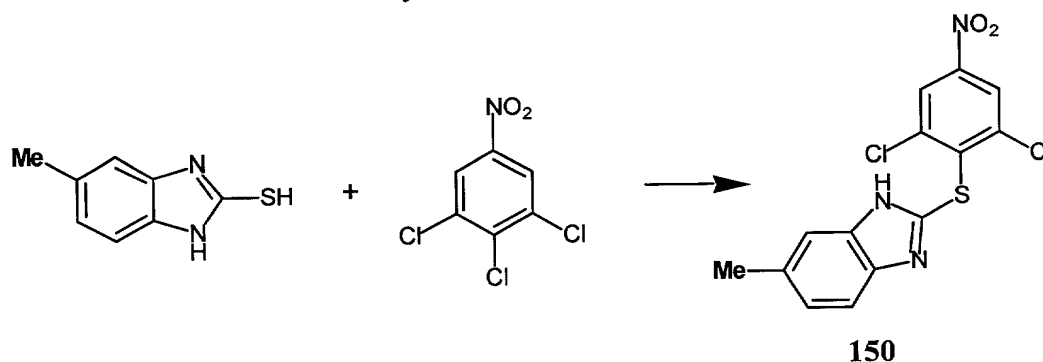
The benzoxazole **149** was formed according to the method of Terashima and Ishi (*Synthesis* 1982, 484-85.). Phenylacetic acid **148** (387 mg, 1.95 mmol), 2-amino-6-chloro-phenol (233 mg, 1.67 mmol, described in *J. Med. Chem.* 1996, 39,

3435-3450), and boric acid (120 mg, 1.95 mmol) were combined in xylenes (24 mL) and the mixture heated to reflux in a flask equipped with a Dean-Stark trap. After 8 h, the reaction mixture was filtered, concentrated, and the residue purified by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate). Fractions containing benzoxazole 149 were concentrated to a yellow solid (419 mg).

^1H NMR (CDCl_3) δ 8.05 (d, 1H); 8.00 (dd, 1H); 7.61 (d, 1H); 7.57 (d, 1H); 7.33 (d, 1H); 7.27 (d, 1H) 4.38 (s, 2H). MS ($\text{M}+\text{H}$) 307.0

EXAMPLE 150

This illustrates the synthesis of compound 150.

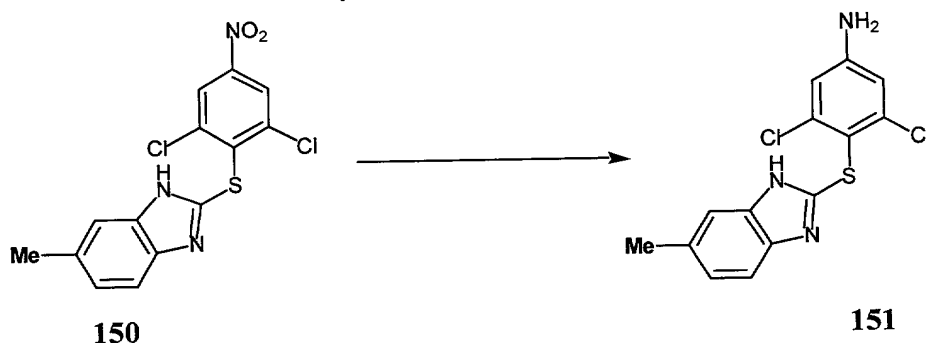


A round-bottomed flask was charged with 2-mercapto-5-methylbenzimidazole (4.84 g, 29.5 mmol), potassium hydroxide (1.66 g, 29.5 mmol), and water (18 mL). This suspension was heated to 120°C for 3.0 hours. Then 3,4,5-trichloronitrobenzene (6.68 g, 29.5 mmol) dissolved in 53 mL of *n*-butanol was added dropwise while the reaction stirred at 120°C. All the white solids went into solution and the solution proceeded to turn a deep red color. The reaction was left stirring for five days, at which point a yellow precipitate was seen. The reaction was then cooled to room temperature and the precipitate was filtered and washed with distilled water to yield 8.10 g (78%) of compound 150 as canary yellow crystals which were a 50/50 mixture of both possible tautomers.

^1H NMR (400MHz) (d_6 -DMSO) δ 12.64 (1H, s); 8.48 (2H, d, $J=2.2$ Hz); 7.34 and 7.27 (1H, 2 tautomeric doublets, $J=8.3$ Hz); 7.26 and 7.19 (1H, 2 tautomeric singlets); 6.99 and 6.95 (1H, 2 tautomeric doublets, $J=8.1$ Hz); 2.38 and 2.35 (3H, 2 tautomeric singlets).

EXAMPLE 151

This illustrates the synthesis of compound **151**.



5 A round-bottomed flask was charged with 8.1 g (22.8 mmol) of compound **150**, 20.6 g (91.4 mmol) of tin dichloride dihydrate, and 150 mL of EtOAc. This was heated to 75°C for 3.0 hours. The reaction was cooled to room temperature, diluted with 300 mL of EtOAc and washed with 250 mL of 2N aqueous KOH solution followed by 200 mL of brine. The organics were dried over sodium sulfate and concentrated to 7.4 g
10 (94%) of **151** as a pale yellow solid that was used without further purification. MS (M+H) 324

EXAMPLE 152

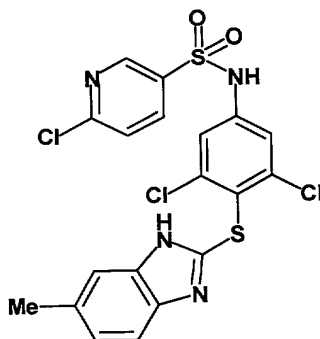
This illustrates the synthesis of compound **152**.

15 A round-bottomed flask was charged with compound **151** (749 mg, 2.31 mmol), 4-acetylbenzenesulfonyl chloride (1.01 g, 4.62 mmol), 2,6-lutidine (496 mg, 4.62 mmol), acetone (4.0 mL), and a catalytic amount of DMAP. This was stirred at room temperature for 12 hours, after which 2,6-lutidine hydrochloride was seen as a white precipitate. The reaction was diluted with 40 mL of EtOAc and washed with 30 mL of
20 1N aqueous HCl followed by 30 mL of brine. The organics were dried over magnesium sulfate and concentrated to a clear oil that was dissolved in 30 mL of THF. To this was added 30 mL of 0.5N aqueous KOH. This was stirred at room temperature for 12 hours, and the reaction color progressed from a light yellow to a deep orange. Next, the pH was brought to 7.0 with 1.0N HCl and the THF was removed *in vacuo*. The remaining
25 aqueous phase was extracted with 100 mL of Et₂O. The organic layer was dried over sodium sulfate and concentrated to a yellow oil that was further purified with silica gel flash chromatography (3:2 hexanes:EtOAc). The desired fractions were combined and concentrated to an oil which was recrystallized from hot EtOAc/hexanes to yield 312 mg (27%) of **152** as an off-white solid. MS (M-H) 504.

^1H NMR (d_6 -DMSO) δ 12.36 (1H, broad s); 11.39 (1H, broad s); 8.18 (2H, t); 8.03 (2H, t); 7.32 (2H, s); 7.32-7.04 (2H, m); 6.96 (1H, m); 2.62 (3H, s); 2.35 (3H, s).

EXAMPLE 153

5 This illustrates the synthesis of compound **153**.

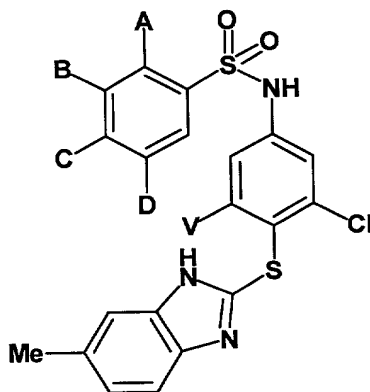


Compound **153** was prepared according to Example 152. In this case, 353 mg (1.1 mmol) of compound **151** was used to give 76 mg (14%) of **153** as white crystals.

^1H NMR (d_6 -DMSO) δ 12.31 (1H, broad s); 11.42 (1H, broad s); 8.90 (1H, d); 8.29 (1H, dd); 7.81 (1H, d); 7.34 (2H, s); 7.26 (1H, broad s); 7.17 (1H, broad s); 6.92 (1H, d); 2.35 (3H, s). MS (M-H) 497.0.

The additional examples of Table 21 were prepared according to the method of Example 152.

Table 21



	V	A	B	C	D	m/e (M-H)
152	Cl	H	H	-C(=O)Me	H	504
20 153	Cl	[2-chloro-5-pyridyl]				497
154	Cl	Me	H	Cl	Me	524

	155	Cl	Cl	H	Cl	H	530
	156	Cl	Cl	H	CF ₃	H	564
	157	Cl	Cl	H	Cl	Me	544
	158	H	Cl	H	Cl	H	496
5	159	H	H	Cl	Cl	H	496
	160	H	Cl	H	CF ₃	H	530
	161	H	Cl	H	Cl	Me	510
	162	H	H	H	I	H	554
	163	H	[2-chloro-5-pyridyl]				463
10	164	H	Me	H	Cl	Me	490

EXAMPLE 154

¹H NMR (*d*₆-DMSO) δ 12.29 (1H, broad s); 11.37 (1H, broad s); 8.01 (1H, s); 7.57 (1H, s); 7.19-7.33 (4H, m); 6.91 (1H, s); 2.57 (3H, s); 2.38 (3H, s); 1.24 (3H, s).
 15 MS (M-H) 524.

EXAMPLE 155

MS (M-H) 529.8. ¹H NMR (*d*₆-DMSO) δ 12.31 (1H, broad s); 11.64 (1H, broad s); 8.18 (1H, d); 7.94 (1H, d); 7.71 (1H, dd); 7.34-7.09 (4H, m); 6.93 (1H, d); 2.33
 20 (3H, s).

EXAMPLE 156

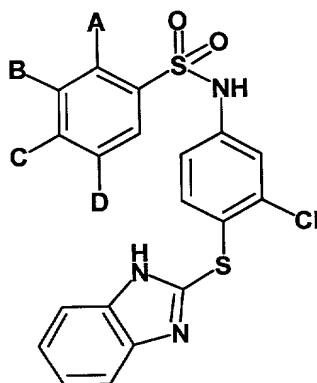
MS (M-H) 564. ¹H NMR (*d*₆-DMSO) δ 12.28 (1H, broad s); 11.80 (1H, broad s); 8.38 (1H, d); 8.19 (1H, s); 8.00 (1H, d); 7.29 (2H, s); 7.24 (1H, broad s); 7.15
 25 (1H, broad s); 6.91 (1H, d); 2.34 (3H, s).

EXAMPLE 157

MS (M-H) 544. ¹H NMR (*d*₆-DMSO) δ 12.29 (1H, broad s); 11.58 (1H, s); 8.22 (1H, s); 7.89 (1H, s); 7.29 (2H, s); 7.24 (1H, broad s); 7.16 (1H, broad s); 6.91
 30 (1H, d); 2.41 (3H, s); 2.34 (3H, s).

The examples of Table 22 were prepared by analogy to the methods of Examples 150-152.

Table 22

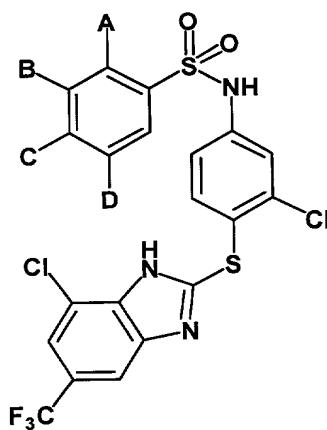


		A	B	C	D	m/e (M-H)
	165	Cl	H	Cl	Me	496
5	166	Cl	H	Cl	H	482
	167	H	H	I	H	540
	168	H	Cl	Cl	H	482
	169	Cl	H	CF ₃	H	516
	170	Me	H	Cl	Me	476

10

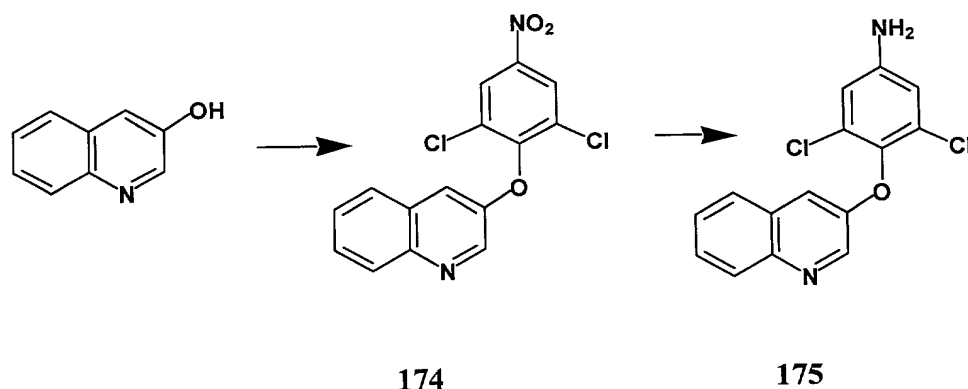
The examples of **Table 23** were prepared by analogy to the methods of Examples 150-152.

Table 23



		A	B	C	D	m/e (M-H)
15	171	Cl	H	Cl	H	584
	172	Cl	H	CF ₃	H	618
	173	Me	H	Cl	Me	578

EXAMPLE 174



5

3-Hydroxyquinoline (prepared according to the procedure of Naumann, *et al.*, *Synthesis*, **1990**, 4, 279-281)) (3 g) and 1,2,3-trichloro-5-nitrobenzene (4.7 g) were dissolved in DMF (80 mL) and heated with cesium carbonate (7.4g) for 2 hr at 60°C. The reaction was poured into ice/water (500 ml). The resulting off-white precipitate was collected by filtration and rinsed with hexane to afford compound 174 as a solid (6.9g) suitable for use in the next reaction.

¹H NMR in CDCl₃ 8.863 (d, J=2.2Hz, 1H), 8.360 (s, 2H), 8.106 (d, J=8.6Hz, 1H), 7.646 (m, 2H), 7.529 (d, J=8.6Hz, 1H), 7.160 (d, J=2.2Hz, 1H)

15

EXAMPLE 175

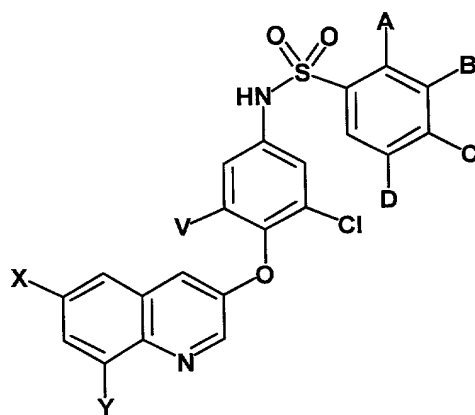
To a solution of compound 180 (6.9 g) in ethanol/THF/water (ratio 40:20:10) was added ammonium chloride (3.3 g) and powdered iron (3.4g). This mixture was heated to reflux for 5 hr. The hot mixture was then filtered through Celite and concentrated. The residue was dissolved in ethyl acetate and washed with saturated NaHCO₃ solution followed by water and then brine. The solution was dried over magnesium sulfate and concentrated to afford compound 175 as an off-white solid (5.6 g).

¹H NMR in (DMSO) δ 8.846 (d, J=2.9Hz, 1H), 8.010 (m, 1H), 7.915 (m, 1H), 7.645 (m, 1H), 7.560 (m, 1H), 7.401 (d, J=2.9Hz, 1H), 6.778 (s, 2H), 5.762 (s, 2H).

25

Treatment of the aniline 175 with various sulfonyl chlorides according to conventional methods gave the sulfonamides of Table 24.

Table 24



Example	X	Y	V	A	B	C	D
176	H	H	Cl	CF ₃	H	Cl	H
5 177	H	H	Cl	Cl	H	CF ₃	H
178	H	H	Cl	Cl	H	Cl	H
179	H	H	Cl	Cl	H	Cl	Me
180	H	H	H	Cl	H	Cl	H
181	-CO ₂ Me	H	Cl	Cl	H	Cl	H
10 182	H	-CO ₂ Me	Cl	Cl	H	Cl	H
183	-CO ₂ H	H	Cl	Cl	H	Cl	H
184	H	-CO ₂ H	Cl	Cl	H	Cl	H
185	Me	H	Cl	Cl	H	Cl	Me
186	H	H	F	Cl	H	Cl	Me

15

EXAMPLE 176

¹H NMR (DMSO) δ 11.4-11.6 (1H, broad), 8.87 (1H, d, *J* = 2.9 Hz), 8.15-8.22 (2H, m), 8.00-8.08 (2H, m), 7.87 (1H, d, *J* = 8.0 Hz), 7.55-7.68 (2H, m), 7.47 (1H, d, *J* = 2.9 Hz), 7.35 (2H, s). MS (M-H) 545. mp 98.8 °C.

20

EXAMPLE 177

¹H NMR(DMSO) δ 11.58 (1H, s), 8.86 (1H, d, *J* = 2.9 Hz), 8.38 (1H, d, *J* = 8.4 Hz), 8.23 (1H, s), 8.01 (1H, d, *J* = 8.4 Hz), 7.86 (1H, d, *J* = 8.1 Hz), 7.53-7.68 (2H, m), 7.46 (1H, d, *J* = 2.9 Hz), 7.34 (2H, s). MS (M-H) 545.0

25

EXAMPLE 178

¹H NMR(d₆-acetone) 9.9 (1H, br s), 8.794 (1H, d, *J* = 2.9 Hz), 8.23 (1H, d, *J* = 8.4 Hz), 8.035 (1H, br d, *J* = 8.4 Hz), 7.793 (1H, d, *J* = 1.5 Hz), 7.78 (1H, m), 7.62-7.70 (2H, m), 7.57 (1H, td, *J* = 6.8, 1.2 Hz), 7.476 (2H, s), 7.364 (1H, d, *J* = 2.6 Hz). MS (M-H) 511.0.

EXAMPLE 179

¹H NMR(300MHz/CDCl₃) δ 2.43(3H, s), 7.10(1H, d, *J* = 3Hz), 7.26(2H, s), 7.48-7.64(4H, m), 7.96(1H, s), 8.09(1H, d, *J* = 8.7Hz), 8.78(1H, d, *J* = 3Hz). MS(M+H) 527. mp 233-235 °

EXAMPLE 180

¹H NMR(300MHz/CDCl₃) δ 7.14(1H, dd, *J* = 2.6Hz, *J* = 8.9Hz), 7.26(1H, d, *J* = 8.9Hz), 7.33(1H, d, *J* = 2.6Hz), 7.56-7.58(2H, m), 7.66-7.69(2H, m), 7.87(1H, m), 7.93(1H, d, *J* = 2.0Hz), 8.00(1H, m), 8.09(1H, d, *J* = 8.5Hz), 8.80(1H, d, *J* = 2.9Hz), 11.06(1H, brs). MS(M+H) 479 mp 122 °C

EXAMPLE 181

3-[2,6-Dichloro-4- (2,4-dichloro-benzenesulfonylamino)-phenoxy]-quinoline-6-carboxylic acid methyl ester (181)

A solution of 3-(4-Amino-2, 6-dichloro-phenoxy)-quinoline-6-carboxylic acid methyl ester (**312**) (0.93mmol) and 2,4-dichlorobenzenesulfonyl chloride (250mg, 1.02mmol) in Pyridine (0.13ml, 1.53mmol)- CH₂Cl₂ (3.7ml) was stirred at room temperature for 12 hr. Sat NaHCO₃ was added to the reaction mixture, which was then extracted twice with AcOEt. Organic layer was washed by brine, dried over anhydrous MgSO₄, and concentrated. Crude residue was purified by column chromatography (Hexane/AcOEt=2/1, 80g of silica gel) to afford compound **181** (237mg, 41%, in 3 steps).

¹H NMR (300MHz,DMSO-d₆) δ 3.90 (3H, s), 7.31(2H, s), 7.72 (1H, dd, *J* = 1.8, 7.8Hz), 7.79 (1H, d, *J* = 3.0Hz), 7.96 (1H, d, *J* = 1.8Hz), 8.11 (2H, s), 8.18 (1H, d, *J* = 7.8Hz), 8.64 (1H, s), 8.99 (1H, d, *J* = 3.0Hz), 11.42 (1H, br s). MS (M+H) 571

EXAMPLE 182

3-[2,6-Dichloro-4- (2,4-dichloro-benzenesulfonylamino)-phenoxy]-quinoline-8-carboxylic acid methyl ester (182)

To a solution of 3-(4-Amino-2, 6-dichloro-phenoxy)-quinoline-8-carboxylic acid methyl ester (**315**) (1.26mmol) in Pyridine (0.15ml, 1.80mmol) and CH₂Cl₂ (5ml), was added 2,4-Dichlorolbenzenesulfonyl chloride (381mg, 1.55mmol). The mixture was stirred at room temperature for 12hr. Sat NaHCO₃ was added to the reaction mixture, which was then extracted twice with AcOEt. Organic layer was washed by Brine, dried over MgSO₄, and concentrated. The crude residue was purified by column chromatography (Hexane/AcOEt=2/1, 80g of silica gel) to afford compound **182** (506mg, 70%) as a white solid.

¹H NMR (300MHz,DMSO-d₆) δ 3.91 (3H, s), 7.31(2H, s), 7.57-7.65 (2H, m), 7.72 (1H, dd, J=2.1, 8.6Hz), 7.83(1H, d, J=8.6Hz), 7.96 (2H, d, J=2.1Hz), 8.03 (1H, d, J=8.6Hz), 8.18 (1H, d, J=8.6Hz), 8.94 (1H, d, J=2.1Hz), 11.4 (1H, br s), MS(M+H) 571

EXAMPLE 183

3-[2,6-Dichloro-4- (2,4-dichloro-benzenesulfonylamino)-phenoxy]-quinoline-6-carboxylic acid (183)

To a solution of 3-[2,6-Dichloro-4- (2,4-dichloro-benzenesulfonylamino)-phenoxy]-quinoline-6-carboxylic acid methyl ester (**181**) (200mg, 0.35mmol) in THF/MeOH(2ml/2ml) was added 4N NaOH (0.1ml, 0.4mmol). This mixture was refluxed for 2.5 hr. The reaction mixture was cooled to room temperature and was neutralized with 2N HCl, and then concentrated. The residue was extracted twice with AcOEt. Organic layer was washed by Brine, dried over anhydrous MgSO₄, and concentrated to give a solid. Crude product was recrystallized by Hexane/AcOEt to afford compound **183**(153mg, 78%).

¹H NMR (300MHz,DMSO-d₆) δ 7.16 (2H, s), 7.62(1H, dd, J=2.0, 8.5Hz), 7.73 (1H, d, J=2.9Hz), 7.82 (1H, s), 8.08-8.11 (3H, m), 8.60 (1H, s), 8.95 (1H, d, J=2.9Hz), 13.2 (1H, br s), MS (M+H) 557. mp 228-2

EXAMPLE 184

3-[2,6-Dichloro-4- (2,4-dichloro-benzenesulfonylamino)-phenoxy]-quinoline-8-carboxylic acid (184)

To a solution of 3-[2,6-Dichloro-4- (2-chloro-4-trifluoromethyl-benzenesulfonylamino)-phenoxy]-quinoline-8-carboxylic acid methyl ester (**183**) (402mg, 0.7mmol) in THF/MeOH=0.1ml/0.3ml was added 4N NaOH (0.2ml, 0.77mmol). The mixture was refluxed for 12hr. After cooling to room temp. the reaction mixture was filtered to remove insoluble materials. The filtrate was concentrated and the residue was dissolved in aq NH₄Cl and extracted twice with AcOEt. Organic layer was washed by Brine, and dried over anhydrous MgSO₄, and concentrated to afford compound **184** (197mg, 50%) as a white solid.

¹H NMR (300MHz,DMSO-d₆) δ 7.32 (2H, s), 7.70-7.81(2H, m), 7.90 (1H, d, J=2.2Hz), 7.96 (1H, d, J=2.2Hz), 8.17-8.19 (1H, m), 8.22-8.24 (1H, m), 8.38-8.39 (1H, m), 9.11 (1H, d, J=2.2Hz), 11.4 (1H, br s), 15.4 (1H, br s), MS (M+H) 557. mp 263-266°C

EXAMPLE 185

2,4-Dichloro-N- [3,5-dichloro-4- (6-methyl-quinolin-3-yloxy)-phenyl]-5-methyl-benzenesulfonamide(185)

To a solution of 3,5-Dichloro-4- (6-methyl-quinolin-3-yloxy)-phenylamine (**339**) (400mg, 1.25mmol) in Pyridine (0.12ml, 1.48mmol)- CH₂Cl₂ (4ml) was added 2,4-Dichloro-5-methylbenzenesulfonyl chloride (325mg, 1.25mmol). The mixture was stirred at room temperature for 12hr. The reaction mixture was concentrated and the residue was purified by column chromatography (Hexane/AcOEt=2/1, 80g of silica gel) to provide compound (**185**) (453mg, 66%) as a white solid.

¹H NMR (300MHz,DMSO-d₆) δ 2.41 (3H, s), 2.44(3H, s), 7.31 (3H, s), 7.49 (1H, d, J=8.7Hz), 7.61 (1H, s), 7.88-7.91 (2H, m), 8.19 (1H, s), 8.74 (1H, d, J=3.0Hz), 11.3 (1H, br s), MS (M+H) 541. mp 228-230°.

EXAMPLE 186

PART 1

Preparation of 3-chloro-5-fluoro-4-(quinolin-3-yloxy)nitrobenzene (**186.1**)

To a solution of 3,4-Difluoronitrobenzene 1.00g in conc.H₂SO₄ (20ml), was added
5 portionwise Cl₂O in CCl₄(25ml, prepared as described by Cady G. H. et. al in Inorg.
Synth. Vol 5, p156(1957)). The mixture was stirred at room temperature overnight. The
mixture was poured into crashed ice and extracted with Et₂O (30mlx3). Combined ether
layers were washed with 10%Na₂SO₃ and brine, and dried over Na₂SO₄. The solvent was
concentrated to Ca. 10ml(This solution contains 3-Chloro-4,5-difluoronitrobenzene).
10 This solution was diluted with acetone (60ml), and then 3-hydroxyquinoline 0.75g and
K₂CO₃ 2.2g were added to this solution. The mixture was heated to reflux for 1.5 hr.
After cooling the reaction mixture was filtered through a short celite pad. The filtrate
was concentrated to give an oil, which was then purified by column chromatography
(silica gel, AcOEt:Hexane=1:5) to provide the intermediate compound **186.1** (0.980g) as
15 a yellow oil.

PART 2

Preparation of 3-Chloro-5-fluoro-4-(quinolin-3-yloxy)phenylamine

(**186.2**)

20 To a solution of 3-Chloro-5-fluoro-4-(quinolin-3-yloxy)nitrobenzene
(**186.1**) (0.980g) and NH₄Cl (1.64g) in EtOH(50ml) – H₂O (5ml), was added iron powder
(1.92g). The mixture was heated to reflux for 1hr. After cooling the reaction mixture
was filtered through short celite pad. The filtrate was concentrated, diluted with sat.
NaHCO₃ and extacted with AcOEt(30mlx3). The combined organic layeres were washed
25 with brine and dried over Na₂SO₄. Concentration of solvent afford crude product, which
was purified by column chromatography (silicagel, AcOEt:Hexane=1:3) to provide
aniline **186.2** (0.420g) as a colorless solid.

PART 3

30 Preparation of N-[3-chloro-5-fluoro-4-(quinolin-3-yloxy)phenyl]-2,4-
dichloro-5-methyl-benzenesulfonamide (**186**)

To a solution of 3-chloro-5-fluoro-4-(quinolin-3-yloxy)phenylamine
(**186.2**) (0.420g) in pyridine(2.2ml), was added 2,4-dichloro-5-
methylbenzenesulfonylchloride 0.360g. The mixture was stirred at room for 1hr. The

reaction mixture was purified directly by column chromatography (silicagel, AcOEt:Hexane=1:3). The product was triturated by hexane to give title compound (0.522g). (73%) as a solid.

NMR(300MHz/ CDCl_3) δ 2.43(3H, s), 7.05(1H, d, $J=2.6\text{Hz}$), 7.09-7.11(1H, m), 7.21(1H, d, $J=2.6\text{Hz}$), 7.36(1H, brs), 7.49-7.66(4H, m), 7.96(1H, s), 8.10(1H, d, $J=8.2\text{Hz}$), 8.80(1H, brs) MS (M+H) 511. mp 187°C

EXAMPLE 187

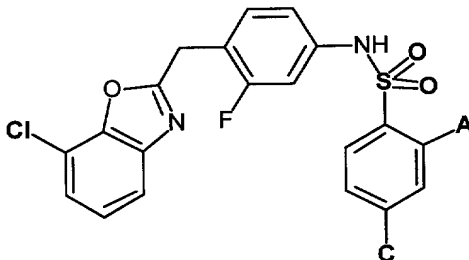
This illustrates the synthesis of 7-chloro-2-(2-fluoro-4-amino-benzyl)-benzoxazole **187**.

To the nitro compound **149** (419 mg, 1.4 mmol) in ethyl acetate (10 mL) was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1.2 g, 5.5 mmol). The reaction mixture was heated to reflux for 30 minutes. After allowing to cool to room temperature, the reaction mixture was poured into 13 mL of saturated 2N $\text{KOH}_{(\text{aq})}$. The layers were separated, and the aqueous layer extracted 1 x 30 mL ethyl acetate. The combined organic layers were washed with saturated brine and dried over Na_2SO_4 . After concentration, the yellow oil was purified by radial chromatography (2 mm silica gel layer Chromatatron plate, 3:2 hexanes:ethyl acetate). Eluant containing the desired product was concentrated to 194 mg of aniline **187**.

^1H NMR (d_6 -acetone) δ 7.58 (dd, 1H); 7.39-7.31 (m, 2H); 7.11 (t, 1H); 6.50-6.43 (m, 2H); 4.94 (bs, 2H); 4.21 (s, 2H). MS (M+H) 277.1.

EXAMPLE 188

This illustrates the synthesis of sulfonamide **188**.



Example **188** A = C=Cl

Example **189** A = H; C = COMe

To aniline **187** (95 mg, 0.34 mmol) in acetone (1 mL) was added 2,6-lutidine (60 μL , 0.51 mmol) and 2,4-dichloro-benzenesulfonyl chloride (93 mg, 0.38

mmol, Maybridge Chemical Co.). After 16 hours, the reaction mixture was filtered through a 1 cm plug of silica gel. After concentration, the yellow oil was purified by radial chromatography (1 mm silica gel layer Chromatatron plate, 3:1 hexanes:ethyl acetate). Eluant containing the product was concentrated and the residue recrystallized from hot hexanes/ethyl acetate. Filtration and drying under vacuum yielded the sulphonamide **188** as light yellow crystals (65 mg).

^1H NMR (d_6 -acetone) δ 9.70 (bs, 1H); 8.16 (d, 1H); 7.71 (d, 1H); 7.60-7.56 (m, 2H); 7.42-7.32 (m, 3H); 7.11-7.09 (m, 2H); 4.32 (s, 2H). MS (M-H) 482.9.

EXAMPLE 189

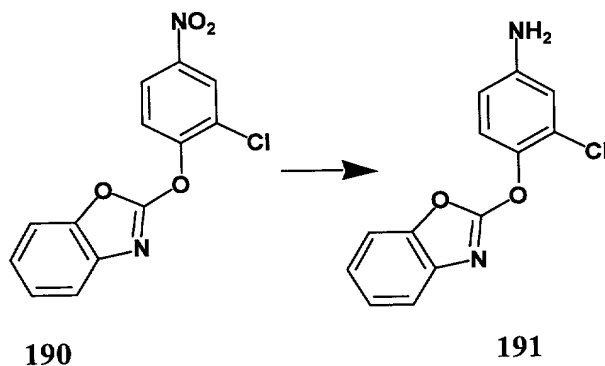
This illustrates the synthesis of sulfonamide **189**.

By the method of example **188**, using the aniline **187** and 4-acetyl-benzenesulfonyl chloride compound **189** was obtained as light yellow crystals.

^1H NMR (d_6 -acetone) δ 9.50 (bs, 1H); 8.11 (d, 2H); 8.11 (d, 2H); 7.98 (d, 2H); 7.57 (d, 1H); 7.42-7.32 (m, 3H); 7.12-7.06 (m, 2H); 4.33 (s, 2H); 2.61 (s, 3H). MS (M-H): 482.9.

EXAMPLE 190

This illustrates the synthesis of compound **190**.



2-chloro-4-nitro-phenol (2 g, 11.5 mmol) was dissolved in DMF (5 mL) and treated with Cs_2CO_3 (3.7 g, 11.5 mmol). The reaction mixture was heated to 50 °C until gas evolution stopped. 2-chlorobenzoxazole (2.65 g, 17.3 mmol) was added, and then the reaction mixture was warmed to 75 °C. After 5 hours, the heat was removed and the reaction mixture was poured into 150 mL of deionized water with vigorous stirring. The precipitate was collected by filtration and rinsed several times with distilled water.

The product was dried under a stream of air for 15 minutes, then under vacuum overnight to afford compound 190 as an off-white solid (3.4 g), homogeneous by TLC ($R_f=0.55$, 3:1 hexanes:ethyl acetate). MS (M+H) 291.0

5

EXAMPLE 191

This illustrates the synthesis of compound 191. See above.

A round-bottomed flask was charged with 2.01 g (6.93 mmol) of compound 190, 50 mL of isopropyl alcohol, and 20 mL of THF. Then 0.5 mL of a 50/50 suspension of Raney Nickel in water was added. The reaction was then stirred under a hydrogen balloon at room temperature for 24 hours. Raney Nickel was removed by
10 filtration through celite, and the solution was concentrated *in vacuo*. Recrystallization from ethanol and hexanes gave 1.01 g (60%) of aniline 191 as off-white needles. MS (M+H) 261.0.

15

EXAMPLE 192

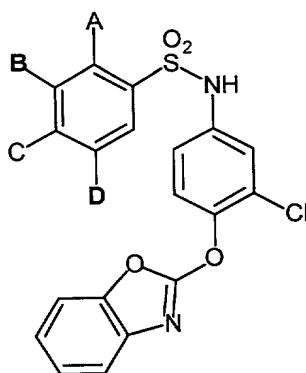
This illustrates the synthesis of compound 192. (See Table below)

A round-bottomed flask was charged with aniline 191 (144 mg, 0.55 mmol), 2,4-dichlorobenzenesulfonyl chloride (221 mg, 0.55 mmol), 2,6-lutidine (97 mg, 0.55 mmol), catalytic DMAP, and acetone (3.0 mL). The reaction was allowed to stir
20 overnight. The reaction was then diluted with 20 mL of methylene chloride and washed with 10 mL of 1N HCl and 10 mL of brine. The organics were dried over Na_2SO_4 and concentrated to a clear oil. This oil was further purified using silica gel flash chromatography. The desired fractions were combined and concentrated to a stiff foam. The product was recrystallized from methylene chloride and hexanes to yield 165 mg
25 (65%) of compound 192 as white crystals.

^1H NMR (d_6 -DMSO) δ 11.21 (1H, s); 8.12 (1H, d, $J=8.6$ Hz); 7.92 (1H, d, $J=2.1$ Hz); 7.69-7.63 (3H, m); 7.48 (1H, dd, $J=7.3, 4.3$ Hz); 7.31-7.29 (3H, m); 7.18 (1H, dd, $J=9.0, 2.6$ Hz). MS (M-H) 467.0

The additional examples of Table 25 were prepared from aniline 191 and
30 the corresponding sulfonyl chloride by the method of example 192.

Table 25



Example	A	B	C	D	(M-H)
192	Cl	H	Cl	H	467
193	Cl	H	Cl	Me	481
194	Me	H	Cl	Me	
195	Cl	H	CF ₃	H	501
196	H	H	-COMe	H	441
197	[2-chloro-5-pyridyl]				434

EXAMPLE 193

¹H NMR (*d*₆-DMSO) δ 11.14 (1H, s); 8.14 (1H, s); 7.87 (1H, s); 7.65-7.61 (2H, m); 7.50-7.48 (1H, m); 7.32-7.28 (3H, m); 7.19 (1H, dd, *J*=8.9, 2.7 Hz); 2.40 (3H, s). MS (M-H) 481

EXAMPLE 194

¹H NMR (*d*₆-DMSO) δ 10.92 (1H, s); 7.94 (1H, s); 7.65-7.60 (2H, m); 7.54 (1H, s); 7.49 (1H, dd, *J*=4.8, 1.6 Hz); 7.31-7.27 (3H, m); 7.16 (1H, dd, *J*=8.9, 2.6 Hz); 2.56 (3H, s); 2.36 (3H, s).

EXAMPLE 195

¹H NMR (*d*₆-DMSO) δ 11.36 (1H, s); 8.32 (1H, d); 8.18 (1H, s); 7.97 (1H, dd); 7.64 (2H, dd); 7.47 (1H, d); 7.31 (3H, m); 7.20 (1H, dd). MS (M-H) 501.

EXAMPLE 196

¹H NMR (400MHz) (*d*₆-DMSO) δ 10.96 (1H, s); 8.15 (2H, dd); 7.97 (2H, d); 7.62 (2H, d); 7.49 (1H, t); 7.31 (3H, m); 7.22 (1H, t); 2.62 (3H, s). MS (M-H) 441.0

EXAMPLE 197

¹H NMR (*d*₆-DMSO) δ 11.04 (1H, s); 8.89 (1H, s); 8.34 (1H, dd); 8.05 (1H, d); 7.87 (1H, d); 7.67 (1H, dd); 7.52 (1H, t); 7.38 (1H, d); 7.25 (1H, t); 7.19 (1H, t);
5 2.62 (3H, s). MS (M-H) 434.0

EXAMPLE 198

Preparation of 3-Chloro-4-(quinolin-3-yloxy)nitrobenzene(198)

To a solution of 3-hydroxyquinoline (1.00g) and 3-chloro-4-fluoronitrobenzene (1.21g) in Acetone(20ml), was added K₂CO₃ (2.86g). The
10 mixture was refluxed for 1hr. After cooling the reaction mixture was filtered through a short celite pad. The filtrate was concentrated to provide compound 198 (2.07g, quant.) as a brown oil.

¹H NMR(300MHz/CDCl₃) δ 7.02(1H, d, J=9.1Hz), 7.61(1H, m), 7.72-
15 7.80(3H, m), 8.10-8.18(2H, m), 8.45(1H, d, J=2.7Hz), 8.82(1H, d, J=2.8Hz).

EXAMPLE 199

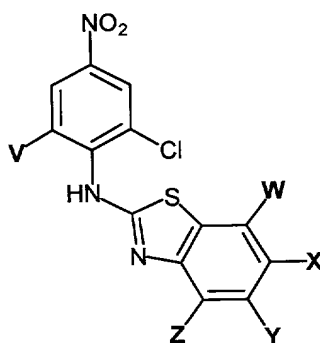
Preparation of 3-Chloro-4-(quinolin-3-yloxy)phenylamine (199)

To a solution of nitrobenzene 198 (2.07g) and NH₄Cl (1.84g) in EtOH
20 (40ml) – H₂O (10 ml), was added iron powder (1.92g). The mixture was heated to reflux for 1hr. After cooling the reaction mixture was filtered through short celite pad. The filtrate was concentrated, diluted with sat. NaHCO₃ (30ml) and extacted with AcOEt(30ml). The combined organic layers were washed with brine (30ml) and dried over Na₂SO₄. Concentration of the solvent afforded the aniline 199 (1.77g,
25 95%) as a yellow solid.

¹H NMR(300MHz/CDCl₃) δ 3.77(2H, brs), 6.63(1H, dd, J=2.7Hz, J=8.6Hz), 6.83(1H, d, J=2.7Hz), 6.99(1H, d, J=8.6Hz), 7.24(1H, d, J=2.8Hz), 7.49(1H, m), 7.56-7.64(2H, m), 8.08(1H, m), 8.86(1H, J=2.8Hz)

The structures for examples 200-208 are illustrated in Table 26.

Table 26



	EXAMPLE	V	W	X	Y	Z	MS(M-H)
5	200	Cl	H	Cl	H	H	372
	201	H	H	H	H	H	304
	203	H	Cl	H	H	Me	352
	204	Cl	Cl	H	Cl	H	406
	205	Cl	H	H	H	Me	354 (M+H)
10	206	Cl	H	Me	H	H	354 (M+H)
	207	Cl	Cl	H	H	H	372
	208	Cl	H	-SO ₂ Me	H	H	416

EXAMPLE 200

15 This illustrates the synthesis of compound **200**.

2-amino-6-chlorobenzothiazole (3.68 g, 20 mmol) and 1,2,3-trichloro-5-nitrobenzene (4.53 g, 20 mmol) were dissolved in anhydrous DMSO (10 mL). Solid K₂CO₃ (3.04 g, 22 mmol) was added and the reaction mixture heated to 150 °C for 4 hours. Let cool, then poured into 200 mL deionized water. A fine yellow solid precipitated which was collected by filtration after attempts to dissolve the product in ethyl acetate failed. The yellow solid was suspended in 100 mL of ethyl acetate and heated to reflux. After cooling to room temperature, filtration, rinsing with ethyl acetate followed by hexanes, and drying under vacuum provided the nitro compound **200** as a yellow powder. (1.06 g)

25 ¹H NMR (*d*₆-DMSO) δ 8.37 (s, 2H); 7.76 (bs, 1H); 7.30 (dd, 1H); 7.23 (bs, 1H). MS (M-H) 372

EXAMPLE 201

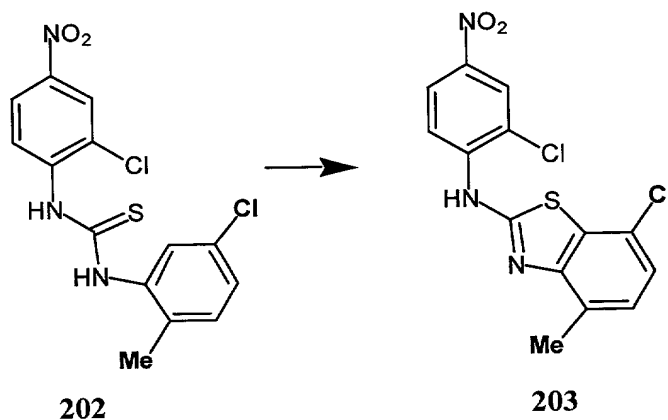
This illustrates the synthesis of compound **201**.

To a solution of 2-chloro-4-nitro aniline (2 g) and potassium t-butoxide (12 mmol) in THF (18 mL) was added a solution of 2-chlorobenzothiazole (2.75 g) in THF (6 mL). The mixture was heated at reflux overnight then quenched into water (100 mL). The product is extracted with methylene chloride and purified by flash chromatography to afford compound **201** (300 mg) as a yellow solid.

^1H NMR (d_6 -acetone) δ 9.74 (br s, 1H), 9.214 (br d, 1H), 8.346 (m, 2H), 7.891 (d, $J=8$ Hz, 1H), 7.794 (d, $J=8$ Hz, 1H), 7.466 (t, $J=7.2$ Hz, 1H), 7.321 (t, $J=7.2$ Hz, 1H). MS (M-H) 304.

EXAMPLE 202

This illustrates the synthesis of compound **202**.



15

By the method of Abuzar et al, (Ind. J. Chem 20B, 230-233 (1981)) 2-chloro-4-nitro phenylisothiocyanate (Lancaster) (0.95g) was coupled with 2-amino-4-chlorotoluene (0.69g) in refluxing acetone to form the mixed thiourea **202** (1.5g).

^1H NMR (DMSO) δ 10.021 (s, 1H), 9.789 (s, 1H), 8.373 (m, 1H), 8.197 (m, 2H), 7.441 (d, $J=1.6$ Hz, 1H), 7.315 (d, $J=8.4$ Hz, 1H), 7.268 (dd, $J=8.4, 2.1$ Hz, 1H), 2.237 (s, 3H). MS (M+H) 356. Anal. calcd.: 47.20 %C, 3.11 %H, 11.80 %N; found: 47.24 %C, 3.15 %N, 11.69%N.

20

EXAMPLE 203

25

This illustrates the synthesis of compound **203**.

To a cool solution of thiourea **202** (0.63 g) in chloroform (6 mL) was added bromine (0.6 g) slowly. The mixture was then heated to reflux for 2 hours. On

cooling, the solids were collected by filtration and then triturated with acetone to afford benzothiazole **203** as its HBR salt (0.5 g).

¹H NMR (DMSO) δ 8.989 (br d, J=8.4 Hz, 1H), 8.365 (d, J=2.4 Hz, 1H), 8.291 (dd, J=9.2, 2.8 Hz, 1H), 7.259 (m, 2H), 5.4 (br s), 2.557 (s, 3H). MS (M-H) 352.
5 Anal. calcd.: for M+0.9HBr: 39.38 %C, 2.34 %H, 9.84 %N; found: 39.44 %C, 2.35 %H, 9.66 %N.

EXAMPLE 204

This illustrates the synthesis of compound **204**.

10 By the method of examples **202** and **203**, 2,6-dichloro-4-nitrophenylisothiocyanate (GB1131780 (1966)) was coupled with 3,5-dichloroaniline to form the corresponding mixed thiourea which was cyclized with bromine to afford benzothiazole **204** suitable for use in the next reaction. MS (M-H) 406

EXAMPLE 205

15 By the method of example **200**, benzothiazole **205** was prepared in 78% yield as a yellow solid. MS (M+H) 354.

EXAMPLE 206

20 By the method of example **200**, benzothiazole **206** was prepared in 30% yield as a yellow solid. MS (M+H) 354

EXAMPLE 207

This illustrates the synthesis of compound **207**.

25 2,7-dichlorobenzothiazole (Example 73.2) (0.85 g, 4.2 mmol) and 2,6-dichloro-4-nitroaniline (2.1 g, 10.4 mmol) were dissolved in anhydrous DMSO (10 mL). Solid Cs₂CO₃ (4.1 g, 12.5 mmol) was added and the reaction mixture heated to 80 °C for 16 hours. Let cool, then poured into 200 mL DI water. Excess cesium carbonate was neutralized with acetic acid. The aqueous layer was extracted 2 x 100 mL of ethyl
30 acetate. The combined organic layers were washed with saturated brine, dried over MgSO₄, filtered, and concentrated to a yellow-brown solid. The insolubility of this compound prevented purification, so the crude material was used directly in the next reaction.

^1H NMR (400MHz) (d_6 -acetone) δ 10.35 (bs, 1H); 8.36 (s, 2H); 7.37 (t, 1H); 7.30 (dd, 1H); 7.21 (dd, 1H). MS (M-H) 371.9.

EXAMPLE 208

5 By the method of examples 202 and 203, 2,6-dichloro-4-nitrophenylisothiocyanate (GB1131780 (1966)) was coupled with methyl-(4-aminophenyl)-sulfone to form the corresponding mixed thiourea which was cyclized with bromine to afford benzothiazole 208 suitable for use in the next reaction.

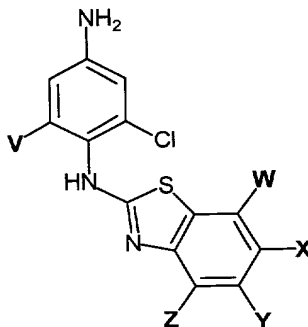
^1H NMR (DMSO) δ 8.44 (s, 2H), 8.28 (br s, 2H), 7.82 (br d, 1H), 7.41 (br d, 1H), 3.19 (s, 3H). MS (M-H) 416.

EXAMPLES 209-216

Reduction of the nitro derivatives of Table 26 by the methods of example 32 or example 175 gave the corresponding anilines illustrated in Table 27.

15 The structures for examples 209-216 are illustrated in Table 27.

Table 27



EXAMPLE	V	W	X	Y	Z	MS(M+H)
20 209	Cl	H	Cl	H	H	344
210	H	H	H	H	H	276
211	H	Cl	H	H	Me	324
212	Cl	Cl	H	Cl	H	378
25 213	Cl	H	H	H	Me	324
214	Cl	H	Me	H	H	324
215	Cl	Cl	H	H	H	344
216	Cl	H - SO ₂ Me	H	H	H	388

EXAMPLE 209

^1H NMR (d_6 -acetone) δ 8.78 (s, 1H); 7.29 (d, 1H); 7.41 (d, 1H); 7.27 (d, 1H); 6.86 (s, 2H); 5.42 (s, 1H). MS (M+H) 344

5

EXAMPLE 212

^1H NMR (DMSO) δ 10.09 (s, 1H), 7.48 (br s, 1H), 7.31 (d, J=1.8 Hz, 1H), 6.72 (s, 2H), 5.91 (br s, 2H). MS (M+H) 378

10

EXAMPLE 215

Crude **207** was reduced with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ according to the procedure of Example **32** to afford compound **215** as a greenish/gray solid after recrystallization from hot ethyl acetate/hexanes (1.14 g).

^1H NMR (d_6 -acetone) δ 8.87 (bs, 1H); 7.40 (dd, 1H); 7.30 (t, 1H); 7.11 (d, 1H); 6.87 (s, 2H); 5.44 (bs, 2H). MS (M+H) 344.0

15

EXAMPLE 216

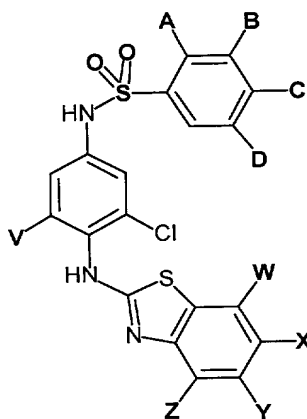
^1H NMR (DMSO) δ 10.08 (s, 1H), 8.31 (s, 1H), 7.76 (d, J=8.4 Hz, 1H), 7.57 (d, J=8.4 Hz, 1H), 6.73 (s, 2H), 5.90 (s, 2H), 3.17 (s, 3H). MS (M-H) 388

20

EXAMPLES 217-238

Sulfonation of the anilines of Table **27** by the methods of example 3 or 192 provides the compounds illustrated in Table **28**.

Table 28



25

Example											
	#	A	B	C	D	V	W	X	Y	Z	MS(M-H)
5	217	Cl	H	Cl	Me	Cl	H	Cl	H	H	564
	218	Cl	H	Cl	H	Cl	H	Cl	H	H	550
	219	Cl	H	CF ₃	H	Cl	H	Cl	H	H	584
	220	Cl	H	Cl	H	H	H	H	H	H	482
	221	Cl	H	CF ₃	H	H	H	H	H	H	516
10	222	Cl	H	Cl	Me	H	H	H	H	H	496
	223	Cl	H	Cl	H	Cl	H	Cl	H	Me	530
	224	Cl	H	CF ₃	H	Cl	H	Cl	H	Me	564
	225	Cl	H	Cl	H	Cl	Cl	H	Cl	H	584
	226	Cl	H	CF ₃	H	Cl	Cl	H	Cl	H	618
15	227	Cl	H	Cl	Me	Cl	Cl	H	Cl	H	598
	228	Cl	H	Cl	H	Cl	H	H	H	Me	530
	229	Cl	H	CF ₃	H	Cl	H	H	H	Me	564
	230	Cl	H	Cl	Me	Cl	H	H	H	Me	544
	231	H	H	-COMe	H	Cl	H	H	H	Me	-
20	232	Cl	H	Cl	H	Cl	H	Me	H	H	530
	233	Cl	H	CF ₃	H	Cl	H	Me	H	H	564
	234	Cl	H	Cl	Me	Cl	H	Me	H	H	544
	235	Cl	H	Cl	H	Cl	Cl	H	H	H	550
	236	Cl	H	CF ₃	H	Cl	Cl	H	H	H	584
	237	Cl	H	Cl	H	Cl	H - SO ₂ Me	H	H	H	594
	238	Cl	H	CF ₃	H	Cl	H - SO ₂ Me	H	H	H	628
25											

EXAMPLE 217

¹H NMR (*d*₆-acetone) δ 9.19 (bs, 1H); 8.51 (s, 1H); 7.74 (d, 1H); 7.72 (s, 1H); 7.43 (s, 2H); 7.37 (d, 1H); 7.28 (dd, 1H); 2.46 (s, 3H). MS (M-H) 563.9

EXAMPLE 218

¹H NMR (*d*₆-acetone) δ 9.19 (bs, 1H); 8.22 (d, 1H); 7.78 (d, 1H); 7.74 (d, 1H); 7.67 (dd, 1H); 7.43 (s, 2H); 7.37 (d, 1H); 7.28 (dd, 1H). MS (M-H) 549.8

EXAMPLE 219

^1H NMR (d_6 -acetone) δ 10.05 (bs, 1H); 9.22 (bs, 1H); 8.45 (d, 1H); 8.06 (s, 1H); 7.98 (d, 1H); 7.73 (m, 1H); 7.45 (s, 2H); 7.36 (d, 1H); 7.28 (dt, 1H). MS (M-H) 583.8.

5

EXAMPLE 223

^1H NMR (DMSO) δ 10.96 (1H, s), 10.11 (1H, s), 8.12-8.22 (1H, broad), 8.06 (1H, d, 8.6), 7.90 (1H, d, $J=2.1$ Hz), 7.65 (1H, dd, $J=8.6, 2.1$ Hz), 7.23 (1H, d, $J=3.5$ Hz), 7.10-7.20 (3H, m), 2.44 (3H, s). MS (M-H) 529.8

10

EXAMPLE 224

^1H NMR (DMSO) δ 11.11 (1H, s), 10.11 (1H, s), 8.27 (1H, d, $J=8.0$ Hz), 8.16 (2H, s), 7.94 (1H, d, $J=8.6$ Hz), 7.10-7.26 (4H, m), 2.43 (3H, s). MS (M-H) 563.9. mp 192.6 °C

15

EXAMPLE 225

^1H NMR (DMSO) δ 11.49 (s, 1H), 10.44 (s, 1H), 8.164 (d, $J=8.4$ Hz, 1H), 7.95 (d, $J=2$ Hz, 1H), 7.71 (dd, $J=8.4, 2\text{Hz}$, 1H), 7.50 (br s, 1H), 7.35 (d, $J=1.6$ Hz, 1H), 7.25 (s, 2H). MS (M-H) 584.

20

EXAMPLE 226

^1H NMR(DMSO) δ 11.59 (s, 1H), 10.40 (s, 1H), 8.368 (d, $J=8.4$ Hz, 1H), 8.20 (br s, 1H), 8.00 (br d, $J=8.4$ Hz, 1H), 7.48 (br s, 1H), 7.344 (t, $J=1.6$ Hz, 1H), 7.274 (d, $J=1.6$ Hz, 2 H). MS (M-H) 618.

25

EXAMPLE 227

^1H NMR (DMSO) δ 11.37 (s, 1H), 10.40 (s, 1H), 8.19 (br s, 1H), 7.90 (m, 1H), 7.53 (br s, 1H), 7.35 (br s, 1H), 7.25 (br s, 2 H), 2.415 (s, 3H). MS (M-H) 598.

30

EXAMPLE 228

^1H NMR (d_6 -DMSO) δ 11.44 (1H, broad s); 9.96 (1H, broad s); 8.33 (1H, d); 8.19 (1H, s); 7.99 (1H, dd); 7.43 (1H, broad s); 7.26 (2H, s); 7.07 (1H, d); 6.97 (1H, t); 2.35 (3H, s). MS (M - H) 529.9.

EXAMPLE 229

^1H NMR(d_6 -DMSO) δ 11.26 (1H, broad s); 9.96 (1H, broad s); 8.12 (1H, d); 7.93 (1H, d); 7.69 (1H, dd); 7.43 (1H, broad s); 7.23 (2H, s); 7.08 (1H, d); 6.97 (1H, t); 2.36 (3H, s). MS (M-H) 564.

EXAMPLE 230

^1H NMR (d_6 -DMSO) δ 11.23 (1H, broad s); 9.96 (1H, broad s); 8.14 (1H, s); 7.88 (1H, s); 7.43 (1H, broad s); 7.24 (2H, s); 7.08 (1H, d); 6.97 (1H, t); 2.40 (3H, s); 2.36 (3H, s). MS (M-H) 543.9.

EXAMPLE 231

^1H NMR (d_6 -DMSO) δ 11.02 (1H, broad s); 9.96 (1H, broad s); 8.16 (2H, d); 7.97 (2H, d); 7.43 (1H, broad s); 7.26 (1H, s); 7.07 (1H, d); 6.97 (1H, t); 2.62 (3H, s); 2.36 (3H, s).

EXAMPLE 232

^1H NMR (d_6 -DMSO) δ 11.28 (1H, broad s); 9.79 (1H, broad s); 8.13 (1H, d); 7.93 (2H, d); 7.70 (1H, dd); 7.44 (1H, broad s); 7.21 (3H, s); 7.05 (1H, d); 2.30 (3H, s). MS (M-H) 529.9.

EXAMPLE 233

^1H NMR (d_6 -DMSO) δ 11.43 (1H, broad s); 9.79 (1H, broad s); 8.34 (1H, d); 8.19 (1H, s); 7.99 (1H, d); 7.44 (1H, broad s); 7.24 (3H, s); 7.04 (1H, d); 2.30 (3H, s). MS (M - H) 564.

EXAMPLE 234

^1H NMR (d_6 -DMSO) δ 11.22 (1H, broad s); 9.79 (1H, broad s); 8.15 (1H, s); 7.89 (1H, s); 7.44 (1H, broad s); 7.23 (3H, s); 7.04 (1H, d); 2.41 (3H, s); 2.31 (3H, s). MS (M - H) 543.9.

EXAMPLE 235

¹H NMR (*d*₆-acetone) δ 9.92 (bs, 1H); 9.35 (bs, 1H); 8.23 (d, 1H); 7.78 (d, 1H); 7.67 (dd, 1H); 7.45 (s, 2H); 7.36-7.29 (m, 2H); 7.16 (dd, 1H). MS (M-H) 549.8.

5

EXAMPLE 236

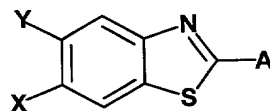
¹H NMR (*d*₆-acetone) δ 8.45 (d, 1H); 8.06 (s, 1H); 7.97 (d, 1H); 7.46 (s, 2H); 7.33-7.29 (m, 2H); 7.16 (dd, 1H). MS (M-H) 583.8.

EXAMPLE 237

10 ¹H NMR (DMSO) δ 11.43 (br s, 1H), 10.40 (br s, 1H), 8.33 (br s, 1H), 8.16 (d, J= 8 Hz, 1H); 7.94 (d, J=2 Hz, 1H), 7.753 (dd, J=8.2, 2 Hz, 1H), 7.71 (dd, J=8.4, 2 Hz, 1H), 7.55 (br s, 1H), 7.265 (s, 2H), 3.22 (s, 3H). MS (M-H) 594.

EXAMPLE 238

15 ¹H NMR (DMSO) δ 11.55 (br s, 1H), 10.40 (br s, 1H), 8.38 (m, 2H), 8.22 (br s, 1H), 8.02 (br d, 1H), 7.77 (dd, J= 8.4, 2 Hz, 1H), 7.55 (br s, 1H), 7.295 (s, 2H), 3.19 (s, 3H). MS (M-H) 628.

Table 29

20

25

Example #	A	X	Y	yield
239	SH	H	CF ₃	92%
240	SH	H	CO ₂ H	66%
241	SH	CN	H	97%
243	SH	H	CN	49%
245	SH	H	Me	53%
250	Cl	H	Cl	96%

EXAMPLE 239

2-Mercapto-5-trifluoromethyl-benzothiazole (239)

In analogy to the procedure of Chaudhuri, N. *Synth. Commun.* **1996**, *26*, 20, 3783, *O*-ethylxanthic acid, potassium salt (Lancaster, 7.5 g, 46.9 mmol) was added to a solution of 2-bromo-5-trifluoromethylphenylamine (Aldrich, 5.0 g, 20.8 mmol) in *N,N*-dimethylformamide (DMF, 30 mL). The mixture was heated to reflux for 4 hours. After cooling to room temperature, the mixture was poured into ice water and acidified with 2N HCl. The solid product was collected by filtration. Recrystallization from CHCl₃/Hexanes gave **239** (4.5 g, 92%) as a white solid.

¹H NMR (400MHz, DMSO-d₆) δ 14.00 (s, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.62 (dd, J = 8.4, 1.0 Hz, 1H), 7.48 (d, J = 1.0 Hz, 1H). MS (M-H) 234.

EXAMPLE 240

2-Mercapto-benzothiazol-5-carboxylic acid (240)

2-Mercapto-benzothiazol-5-carboxylic acid (**240**) (3.5 g, 66%) was synthesized from 4-chloro-3-nitro-benzoic acid, obtained from Fluka, and potassium dithiocarbonate *O*-ethyl ester, obtained from Lancaster, according to the procedure of Chaudhuri, N. *Synth. Commun.* **1996**, *26*, 20, 3783.

¹H NMR (400MHz, DMSO-d₆) δ 14.0 (s, 1H), 13.3 (bs, 1 H), 7.85-7.79 (m, 3 H).

EXAMPLE 241

2-Mercapto-benzothiazole-6-carbonitrile (241)

The title compound was prepared using the method of example 239, starting with 4-amino-3-chloro-benzonitrile (Lancaster, 5.0 g, 32.7 mmol), *O*-ethylxanthic acid, potassium salt (Lancaster, 11.8 g, 73.7 mmol) in DMF (40 mL). The mercaptobenzothiazole (**241**) (6.1 g, 97%) was obtained as a pale brown solid.

¹H NMR (DMSO-d₆) δ 14.10 (s, 1H), 8.22 (d, J = 1.3 Hz, 1H), 7.82 (dd, J = 8.4, 1.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H). MS (M-H) 191.

EXAMPLE 242

3-Amino-4-chloro-benzonitrile (242)

The title compound was prepared using the method of example 32, starting with 4-chloro-3-nitro-benzonitrile (Fluka, 11.0 g, 60 mmol), tin chloride dihydrate (Aldrich, 67.8 g, 300 mmol). 9.0 g (98%) of crude compound **242** was obtained as a yellowish solid.

^1H NMR (DMSO- d_6) δ 7.39 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 2.0 Hz, 1H), 6.93 (dd, J = 8.2, 2.0 Hz, 1H), 5.88 (s, 2H). MS (M-H) 151.

EXAMPLE 243

2-Mercapto-benzothiazole-5-carbonitrile (243)

The title compound was prepared using the method of example 239, starting with 3-amino-4-chloro-benzonitrile (**242**) (9.0 g, 59.0 mmol), *O*-ethylxanthic acid, potassium salt (Lancaster, 21.23 g, 132.7 mmol) in DMF (90 mL). 5.6 g (49%) of compound **243** was obtained as a pale brown solid.

^1H NMR (DMSO- d_6) δ 14.10 (br s, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.70 (dd, J = 8.3, 1.1 Hz, 1H), 7.60 (br s, 1H). MS (M-H) 191.

EXAMPLE 244

2-Bromo-5-methyl-phenylamine (244)

The title compound was prepared using the method of example 32, starting with 1-bromo-4-methyl-2-nitro-benzene (Lancaster, 10.1 g, 46.7 mmol), tin chloride dihydrate (Aldrich, 52.8 g, 233 mmol). 8.2 g (94%) of crude compound **244** was obtained as a pale brown oil.

^1H NMR (DMSO- d_6) δ 7.18 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 2.1 Hz, 1H), 6.93 (dd, J = 8.1, 1.8 Hz, 1H), 5.34 (s, 2H), 2.26 (s, 3H). MS (M+H) 186.

EXAMPLE 245

2-Mercapto -5-Methyl-benzothiazole (245)

The title compound was prepared using the method of example 239, starting with 2-bromo-5-methyl-phenylamine (**244**) (4.48 g, 24.0 mmol), *O*-ethylxanthic acid, potassium salt (Lancaster, 8.70 g, 54 mmol) in DMF (35 mL). The mercaptobenzothiazole **245** was obtained as a pale brown solid (2.31 g, 53%).

^1H NMR (DMSO- d_6) δ 13.70 (br s, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.15-7.10 (m, 2H), 2.38 (s, 3H). MS (M-H) 180.

EXAMPLE 246 & 247

5 **2,3-Dichloro-5-nitrobenzoic acid (246)**

2,3-Dichlorobenzoic acid, obtained from Aldrich, (40 g, 0.21mole) was added portion wise to a -20°C concentrated H_2SO_4 , obtained from Acros, (233 mL) solution which was fitted with a mechanical overhead stirrer. During the addition process, a separate flask containing concentrated H_2SO_4 (50 mL) was cooled to 0°C and
10 fuming HNO_3 , obtained from Acros, (16.6 mL) was slowly added. This solution was then added dropwise to the 2,3-Dichlorobenzoic acid solution at a rate which kept the reaction mixture at or slightly below -15°C . After the addition was complete the resulting solution was allowed to warm to 10°C over 3 hours. The crude solid material was filtered through a fritted filter funnel, washed with cold H_2O (200 mL), and dried under a
15 stream of air followed by high vacuum to yield 21.7 g (44%) of product (246) which contained 4% of the undesired regioisomer (2,3-Dichloro-6-nitrobenzoic acid 247) based on ^1H NMR analysis. The filtrate was slowly poured over ice and additional solid precipitated. This solid was observed to be a 3:1 mixture of 2,3-dichloro-6-nitrobenzoic acid (247) to 2,3-dichloro-5-nitrobenzoic acid (246) based on ^1H NMR analysis.

20 2,3-Dichloro-5-nitrobenzoic acid (246): ^1H NMR (DMSO- d_6) δ 8.63 (d, J = 2.7 Hz, 1H), 8.47 (d, J = 2.7 Hz, 1H). 2,3-Dichloro-6-nitrobenzoic acid: (247). ^1H NMR (DMSO- d_6) δ 8.22 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H).

EXAMPLE 248

25 **1-(2,3-Dichloro-5-nitro-phenyl)-ethanone (248)**

To thionyl chloride, obtained from Aldrich, (125 mL) at 0°C was slowly added 2,3-Dichloro-5-nitrobenzoic acid (246) (21.7 g, 91.9 mmol). The ice bath was taken away and the resulting solution was heated to reflux for 17 hours (note: acid completely dissolves upon heating). After cooling to ambient temperature, the excess
30 thionyl chloride was removed under vacuum and the resulting acid chloride was allowed to stand under high vacuum for 15 h and used in the next step without further purification. To a 1M solution of NaH, 60% oil dispersion obtained from Aldrich, (11.39 g, 285 mmol) in DMF at 0°C was slowly added diethylmalonate, obtained from Aldrich, (14.65 mL,

96.5 mmol) dropwise and the resulting solution was allowed to stir for 30 minutes. The acid chloride was dissolved in DMF (184 mL) and slowly added via cannula to the reaction mixture. The resulting solution was then allowed to stir for 16 h as ambient temperature was reached followed by recooling to 0 °C and slowly quenching with excess 2M aqueous HCl (200 mL). To the crude reaction was added H₂O (500 mL) and EtOAc (500 mL). The aqueous layer was extracted three times with EtOAc (500 mL), the organic layers were combined, washed four times with saturated aqueous brine (500 mL), dried over Na₂SO₄, and concentrated under vacuum to yield an oil which was used in the next step without further purification. The resulting product was dissolved in 111 mL of a 7.7/5/1 AcOH/H₂O/conc. H₂SO₄, solution and heated to reflux for 22 hours. The AcOH was removed under vacuum followed by EtOAc addition (200 mL). The solution was neutralized using 2M aqueous NaOH, extracted 3 times with EtOAc (200 mL). The combined organic layers were washed twice with saturated aqueous brine (200 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was purified by column chromatography (30% CH₂Cl₂ in hexane) to yield 17.6 g (82%) of ketone **248** as a light brown solid.

¹H NMR (DMSO-d₆) δ 8.61 (d, J = 2.6 Hz, 1H), 8.48 (d, J = 2.6 Hz, 1H), 2.65 (s, 3H).

EXAMPLE 249

2-Methoxy-4-nitrobenzenethiol (249)

2-Methoxy-4-nitrobenzenethiol (**249**) was prepared according to the method of Price and Stacy, *J. Amer. Chem. Soc.* 68, 498-500 (1946)) in 67% yield from 1-chloro-2-methoxy-4-nitro-benzene, obtained from Aldrich.

¹H NMR (DMSO-d₆) δ 7.8 (bd, J = 8.4 Hz, 1H), 7.73 (bs, 1H), 7.62 (bd, J = 8.4 Hz, 1H), 5.8 (bs, 1H), 3.95 (s, 3H). MS (M-H) 184.

EXAMPLE 250

2,5-Dichloro-benzenethiazole(250)

5-Chloro-benzenethiazole-2-thiol, obtained from Aldrich, (2 g, 9.9 mmol) was added slowly to sulfuryl chloride, obtained from Aldrich, (20 mL) and stirred for 1 h followed by heating to 50 °C for 15 minutes. The mixture was cooled, poured slowly over ice water and stirred for 30 minutes. The product precipitated out of solution as a

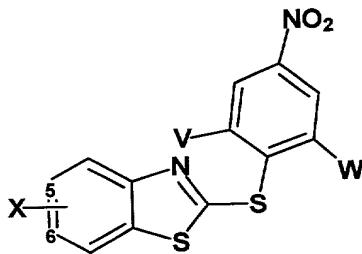
yellow solid and was collected by vacuum filtration and dried under a stream of air followed by high vacuum to give 1.92 g (96%) of compound **250**.

^1H NMR (400MHz, DMSO- d_6) δ 8.18 (d, J = 8.7 Hz, 1H), 8.1 (d, J = 2.0, 1H), 7.59 (dd, J = 8.7, 2.1 Hz, 1H).

5

Table 30

Table 30 illustrates the structures of examples **251-264**.



	#	X	V	W	Yield
10	251	5-Cl	Cl	-COMe	52%
	252	5-CF ₃	Cl	H	92%
	253	5-CO ₂ H	Cl	H	66%
	254	5-CO ₂ Me	Cl	H	100%
	255	5-CO ₂ H	Cl	Cl	100%
15	256	5-CO ₂ Me	Cl	Cl	100%
	257	5-Cl	H	-OMe	75%
	258	5-CF ₃	Cl	Cl	99%
	259	5-CF ₃	Cl	-COMe	75%
	260	6-CN	Cl	Cl	99%
20	261	6-CN	Cl	H	93%
	262	5-CN	Cl	Cl	99%
	263	5-CN	Cl	H	92%
	264	5-Me	Cl	-COMe	98%

25

EXAMPLE 251

1-[3-Chloro-2-(5-chloro-benzothiazol-2-ylsulfanyl)-5-nitro-phenyl]-ethanone (251)

To a 0.55M solution of 5-chloro-2-mercaptobenzothiazole, obtained from Aldrich, (5.55 g, 27.5 mmol) in DMF at ambient temperature was added NaH, 60% oil

dispersion obtained from Aldrich, (1.2 g, 30.0 mmol) portionwise followed by 1-(2,3-Dichloro-5-nitro-phenyl)-ethanone (**248**) (5.83 g, 25 mmol). The reaction solution turned from bright orange to deep red upon acetophenone addition and was heated to 60 °C for 1 hour. The mixture was allowed to cool for a couple of minutes and the product was precipitated out of solution by the slow addition of H₂O (250 mL). After 1h of stirring the product was collect by vacuum filtration using a buchner funnel, dried under a stream of air for 3h, and triterated with a 1:1 MeOH/CH₂Cl₂ solution (200 mL) to yield 5.2 g (52%) of **251** as an orange solid. An additonal 3.77 g (39%) could be isolated by purifying the mother liquor using column chromatography (dry load, 100% CH₂Cl₂).

¹H NMR (DMSO-d₆) δ 8.68 (d, J = 2.5 Hz, 1H), 8.6 (d, J = 2.4 Hz, 1H), 8.05 (d, = 8.6 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 8.6, 2.0 Hz, 1H), 2.65 (s, 3H).

EXAMPLE 252

2-(2-Chloro-4-nitro-phenylsulfanyl)-5-trifluoromethyl-benzothiazole (252)

2-(2-Chloro-4-nitro-phenylsulfanyl)-5-trifluoromethyl-benzothiazole (**252**) was prepared (92%) from 2-chloro-1-fluoro-4-nitrobenzene, obtained from Aldrich, and 5-trifluoromethyl-benzothiazol-2-thiol (**239**) in a similar manner as described in example 251.

¹H NMR (DMSO-d₆) δ 8.58 (d, J = 2.4 Hz, 1H), 8.38-8.32 (m, 2 H), 8.05 (d, = 8.6 Hz, 1H), 8.28 (dd, J = 8.7, 2.5 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.8 (bd, J = 9.9 Hz, 1H).

EXAMPLE 253

2-(2-chloro-4-nitro-phenylsulfanyl)-benzothiazol-5-carboxylic acid (253)

2-(2-chloro-4-nitro-phenylsulfanyl)-benzothiazol-5-carboxylic acid was prepared (66%) from 2-mercapto-benzothiazol-5-carboxylic acid (**240**) and 2-chloro-1-fluoro-4-nitrobenzene, obtained from Aldrich, in a similar manner as described in example 251.

¹H NMR (DMSO-d₆) δ 8.56 (d, J = 2.4 Hz, 1H), 8.42 (bs, 1 H), 8.27 (dd, = 8.7, 2.4 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.7 Hz, 1H), 8.0 (dd, J = 8.4, 1.4 Hz, 1H). MS (M-H) 365.

EXAMPLE 254

2-(2-Chloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (254)

To a 0.25M solution of 2-(2-chloro-4-nitro-phenylsulfanyl)-benzothiazol-5-carboxylic acid (253), (1.38 g, 3.8 mmol) in 10% MeOH in THF was added a 2M solution of (trimethylsilyl)diazomethane in hexane, obtained from Aldrich, (2.1 mL, 4.18 mmol) and the resulting solution was allowed to stir for 18 hours. The crude reaction mixture was concentrated under vacuum to yield 1.4 g (100%) of ester 254 which was taken on without further purification.

¹H NMR (DMSO-d₆) δ 8.6 (d, J = 2.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1 H), 8.28 (dd, = 8.7, 2.5 Hz, 1H), 8.24 (d, J = 8.5 Hz, 1H), 8.1 (d, J = 8.7 Hz, 1H), 8.0 (dd, J = 8.4, 1.4 Hz, 1H), 3.9 (s, 3H).

EXAMPLE 255

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid (255)

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid (255) was prepared (100%) from 2-mercapto-benzothiazol-5-carboxylic acid (240) and 1,2,3-trichloro-5-nitrobenzene, obtained from Aldrich, in a similar manner as described in example 251.

¹H NMR (DMSO-d₆) δ 11.2 (bs, 1H), 8.6 (s, 2H), 8.31 (d, J = 1.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.94 (dd, J = 8.5, 1.4 Hz, 1H). MS (M-H) 399

EXAMPLE 256

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (256)

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (256) was prepared (100%) from 2-(2,6-dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid 255 in a similar manner as described in example 254.

¹H NMR (400MHz, DMSO-d₆) δ 8.6 (s, 2H), 8.33 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.95 (dd, J = 8.4, 1.6 Hz, 1H), 3.9 (s, 3H).

EXAMPLE 257

5-Chloro-2-(2-methoxy-4-nitro-phenylsulfanyl)-benzothiazole (257)

5-Chloro-2-(2-methoxy-4-nitro-phenylsulfanyl)-benzothiazole (257) was prepared (75%) from 2-methoxy-4-nitrobenzenethiol (249) and 2,5-dichlorobenzothiazole (250), in a similar manner as described in example 251.

¹H NMR (DMSO-d₆) δ 8.05 (bd, J = 8.6 Hz, 1H), 8.03 (d, J = 2.0, 1H), 7.99-7.94 (m, 3H), 7.48 (dd, J = 8.6, 2.1 Hz, 1H), 3.95 (s, 3H).

EXAMPLE 258

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-5-trifluoromethyl-benzothiazole (258)

To a solution of 2-mercapto-5-trifluoromethyl-benzothiazole (239) (470 mg, 2.0 mmol) in DMF (20 mL) was added NaH (Aldrich, 60% suspension in hexanes, 80 mg, 2.0 mmol). After the resulting mixture was stirred at ambient temperature for 20 minutes, was added 1,2,3-trichloro-5-nitrobenzene (Acros, 452 mg, 2.0 mmol). The mixture was then heated at 60 °C for 4 hours. After cooled to room temperature, the mixture was poured to water and stirred for 1 hour. The solid product was collected by vacuum filtration to give 258 as a pale yellow solid (840 mg, 99%) which was used in the next reaction without further purification.

¹H NMR (DMSO-d₆) δ 8.61 (s, 2H), 8.27 (d, J = 8.4 Hz, 1H), 7.21 (br s, 1H), 7.74 (dd, J = 8.4, 1.5 Hz, 1H). MS (M+H) 425.

EXAMPLE 259

1-[3-Chloro-5-nitro-2-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone (259)

The title compound was prepared using the method of example 258, starting with 5-trifluoromethyl-benzothiazole-2-thiol (239) (470 mg, 2.0 mmol), 1-(2,3-dichloro-5-nitro-phenyl)-ethanone (248) (466 mg, 2.0 mmol) and NaH (Aldrich, 60% suspension, 80 mg, 2.0 mmol) in DMF (20 mL). Compound 259 (750 mg, 87%) was obtained as a yellow solid.

¹H NMR (DMSO-d₆) δ 8.68 (d, J = 2.6 Hz, 1H), 8.62 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.20 (br s, 1H), 7.74 (dd, J = 8.5, 1.7 Hz, 1H), 2.65 (s, 3H). MS (M+H) 433.

5

EXAMPLE 260

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-6-carbonitrile (260)

The title compound was prepared using the method of example 258, starting with 2-mercapto-benzothiazole-6-carbonitrile (**241**) (960 mg, 5.0 mmol), 1,2,3-trichloro-5-nitrobenzene (Acros, 1.13 g, 5.0 mmol) and NaH (Aldrich, 60% suspension, 200 mg, 5.0 mmol) in DMF (25 mL). Compound **260** (1.9 g, 99%) was obtained as a yellow solid.

¹H NMR (DMSO-d₆) δ 8.61 (s, 2H), 8.58 (d, J = 1.8 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.88 (dd, J = 8.5, 1.8 Hz, 1H).

15

EXAMPLE 261

2-(2-Chloro-4-nitro-phenylsulfanyl)-benzothiazole-6-carbonitrile (261)

The title compound was prepared using the method of example 258, starting with 2-mercapto-benzothiazole-6-carbonitrile (**241**) (960 mg, 5.0 mmol), 2-chloro-1-fluoro-4-nitrobenzene (Aldrich, 878 mg, 5.0 mmol) and NaH (Aldrich, 60% suspension, 200 mg, 5.0 mmol) in DMF (25 mL). Compound **261** (1.62 g, 93%) was obtained as a yellow solid.

¹H NMR (DMSO-d₆) δ 8.62 (d, J = 1.5 Hz, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.29 (dd, J = 8.6, 2.4 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.91 (dd, J = 8.5, 1.6 Hz, 1H). MS (M+H) 348.

25

EXAMPLE 262

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carbonitrile (262)

The title compound was prepared using the method of example 258, starting with 2-mercapto-benzothiazole-5-carbonitrile (**243**) (960 mg, 5.0 mmol), 1,2,3-trichloro-5-nitrobenzene (Acros, 1.13 g, 5.0 mmol) and NaH (Aldrich, 60% suspension,

30

200 mg, 5.0 mmol) in DMF (25 mL). Compound **262** (1.9 g, 99%) was obtained as a yellow solid.

^1H NMR (DMSO- d_6) δ 8.62 (s, 2H), 8.38 (d, J = 1.2 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.88 (dd, J = 8.4, 1.5 Hz, 1H).

5

EXAMPLE 263

2-(2-Chloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carbonitrile (263)

The title compound was prepared using the method of example 258, starting with 2-mercapto-benzothiazole-5-carbonitrile (**243**) (960 mg, 5.0 mmol), 2-chloro-1-fluoro-4-nitrobenzene (Aldrich, 878 mg, 5.0 mmol) and NaH (Aldrich, 60% suspension, 200 mg, 5.0 mmol) in DMF (25 mL). Compound **263** (1.60 g, 92%) was obtained as a yellow solid.

^1H NMR (400MHz, DMSO- d_6) δ 8.56 (d, J = 2.4 Hz, 1H), 8.49 (d, J = 1.2 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.29 (dd, J = 8.7, 2.5 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.85 (dd, J = 8.5, 1.5 Hz, 1H). MS (M+H) 348.

15

EXAMPLE 264

1-[3-Chloro-2-(5-methyl-benzothiazol-2-ylsulfanyl)-5-nitro-phenyl]-ethanone (264)

The title compound was prepared using the method of example 258, starting with 5-methyl-benzothiazole-2-thiol (**245**) (1.90 g, 10.5 mmol), 1-(2,3-dichloro-5-nitro-phenyl)-ethanone (**248**) (2.45 g, 10.5 mmol) and NaH (Aldrich, 60% suspension, 420 mg, 10.5 mmol) in DMF (20 mL). Compound **264** (3.87 g, 98%) was obtained as a yellow solid.

^1H NMR (400MHz, DMSO- d_6) δ 8.65 (d, J = 2.3 Hz, 1H), 8.58 (d, J = 2.5 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.67 (br s, 1H), 7.24 (dd, J = 8.2, 1.5 Hz, 1H), 2.65 (s, 3H), 2.41 (s, 3H). MS (M+H) 379.

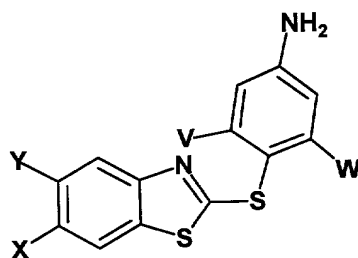
25

Examples 265-276: Reduction of the compounds of Table 30 provides the compounds illustrated in Table 31.

30

Table 31

Table 31 illustrates the structures of examples 265-276



#	X	Y	V	W	Yield
265	H	Cl	Cl	COMe	83%
266	H	CF ₃	Cl	H	97%
267	H	CO ₂ Me	Cl	H	96%
268	H	CO ₂ Me	Cl	Cl	93%
269	H	Cl	H	OMe	100%
270	H	CF ₃	Cl	Cl	96%
271	H	CF ₃	Cl	COMe	100%
272	CN	H	Cl	Cl	98%
273	CN	H	Cl	H	93%
274	H	CN	Cl	Cl	80%
275	H	CN	Cl	H	93%
276	H	Me	Cl	COMe	68%

EXAMPLE 265

1-[5-Amino-3-chloro-2-(5-chloro-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone (265)

To a 0.14M solution of 1-[3-Chloro-2-(5-chloro-benzothiazol-2-ylsulfanyl)-5-nitro-phenyl]-ethanone (**251**) (4.08 g, 10.26 mmol) in a 2:2:1 solution of EtOH, obtained from gold shield, THF, obtained from Aldrich, H₂O was added NH₄⁺Cl⁻, obtained from Aldrich, (2.74 g, 51.29 mmol) followed by iron(0) powder, obtained from Aldrich, (2.86 g, 51.29 mmol). The resulting solution was heated to reflux for 2.5 h with vigorous stirring. TLC and mass spectral analysis showed starting material and hydroxyl amine intermediate so an additional 5 Eq. of both NH₄⁺Cl⁻ and iron powder were subsequently added and the reaction mixture was allowed to continue to reflux for an additional 1.75 hours. The hot solution was immediately filtered through a plug of celite and the celite was washed with copious amounts of EtOAc. The organic layer was concentrated under vacuum, resuspended in EtOAc (100 mL) and NaHCO₃ (100mL), and

extracted 3 times with EtOAc (100 mL). The organic layer was washed twice with saturated aqueous brine (100 mL), dried over Na₂SO₄, concentrated under vacuum, and purified by column chromatography (10-50% EtOAc in hexane) to yield compound **265** (3.14 g, 83%) as a yellow solid.

5 ¹H NMR (DMSO-d₆) δ 7.95 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.39 (dd, J = 8.6, 2.1 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.41 (s, 2H), 2.45 (s, 3H). MS (M+H) 369.

EXAMPLE 266

10 **3-Chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl amine (266)**

3-Chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenylamine (**266**) was prepared (97%) from 2-(2-Chloro-4-nitro-phenylsulfanyl)-5-trifluoromethyl-benzothiazole (**252**), in a similar manner as described in example 90.

15 ¹H NMR (DMSO-d₆) δ 8.2-8.12 (m, 2 H), 7.65 (dd, J = 8.5, 1.7 Hz, 1 H), 7.52 (d, J = 8.5 Hz, 1H), 6.9 (d, J = 2.4 Hz, 1H), 6.7 (dd, J = 8.5, 2.4 Hz, 1H), 6.25 (bs, 2 H). MS (M-H) 359.

EXAMPLE 267

20 **2-(4-Amino-2-chloro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (267)**

2-(4-Amino-2-chloro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (**267**) was prepared (96%) from 2-(2-Chloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (**254**) by the method of example 90.

25 ¹H NMR (DMSO-d₆) δ 8.3 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1 H), 7.88 (dd, J = 8.4, 1.6 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.65 (dd, J = 8.5, 2.4 Hz, 1H), 3.9 (s, 3H). MS (M-H) 349.

EXAMPLE 268

30 **2-(4-Amino-2,6-dichloro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester(268)**

2-(4-Amino-2,6-dichloro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (**268**) was prepared (93%) from 2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-

benzothiazole-5-carboxylic acid methyl ester (**256**) in a similar manner as described in example 90.

^1H NMR (DMSO- d_6) δ 8.34 (d, J = 1.2 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 8.4, 1.6 Hz, 1H), 6.9 (s, 2H), 6.5 (s, 2H), 3.9 (s, 3H). MS (M-H) 383.

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EXAMPLE 269

4-(5-Chloro-benzothiazol-2-ylsulfanyl)-3-methoxy-phenylamine (269)

4-(5-Chloro-benzothiazol-2-ylsulfanyl)-3-methoxy-phenylamine (**269**) was prepared (100%) from 5-chloro-2-(2-methoxy-4-nitro-phenylsulfanyl)-benzothiazole (**257**), by the method of example 265.

^1H NMR (400MHz, DMSO- d_6) δ 7.9 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 2.0, 1H), 7.34 (dd, J = 8.5, 2.0 Hz, 1H), 7.3 (d, J = 8.3 Hz, 1H), 6.39 (d, J = 2.0 Hz, 1H), 6.29 (dd, J = 8.3, 2.1 Hz, 1H), 5.93 (s, 2H), 3.7 (s, 3H). MS (M+H) 323.

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EXAMPLE 270

3,5-Dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenylamine (270)

To a solution of 2-(2,6-dichloro-4-nitro-phenylsulfanyl)-5-trifluoromethyl-benzothiazole (**258**) (840 mg, 1.98 mmol) in EtOAc (20 mL) was added tin chloride dihydrate (Aldrich, 2.15 g, 9.52 mmol) and the resulting mixture was heated to reflux for 3 hours. After cooled to room temperature, to the mixture was added excess of 4N aqueous NaOH solution and the resulting mixture was stirred for 20 minutes. The mixture was filtered through Celite pad and washed with EtOAc. The organic layer was separated, washed twice with a brine solution, dried over Na_2SO_4 , and concentrated under vacuum to give compound **270** (755 mg, 96%) product as a pale yellow solid, which was used in the next reaction without further purification.

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^1H NMR (DMSO- d_6) δ 8.20-8.15 (m, 2H), 7.66 (dd, J = 8.4, 1.7 Hz, 1H), 6.88 (s, 2H), 6.50 (s, 2H). MS (M+H) 395.

30

EXAMPLE 271

1-[5-Amino-3-chloro-2-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone (271)

The title compound was prepared using the method of example 270, starting with 1-[3-chloro-5-nitro-2-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-

ethanone (259) (750 mg, 1,67 mmol), tin chloride dihydrate (Aldrich, 1.89 g, 8.37 mmol). Compound 271 (755 mg, 100%) was obtained as a yellowish solid.

¹H NMR (DMSO-d₆) δ 8.20-8.13 (m, 2H), 7.66 (dd, J = 8.4, 1.0 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.43 (s, 2H), 2.48 (s, 3H). MS (M+H) 403.

EXAMPLE 272

2-(4-Amino-2,6-dichloro-phenylsulfanyl)-benzothiazole-6-carbonitrile

(272)

The title compound was prepared using the method of example 270, starting with 2-(2,6-dichloro-4-nitro-phenylsulfanyl)-benzothiazole-6-carbonitrile (260) (1.9 g, 4.97 mmol), tin chloride dihydrate (Aldrich, 5.62 g, 24.9 mmol). Compound 272 (1.72 g, 98%) was obtained as a yellowish solid.

¹H NMR (400MHz, DMSO-d₆) δ 8.48 (d, J = 1.5 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.86 (dd, J = 8.5, 1.7 Hz, 1H), 6.88 (s, 2H), 6.53 (s, 2H). MS (M+H) 352.

EXAMPLE 273

2-(4-Amino-2-chloro-phenylsulfanyl)-benzothiazole-6-carbonitrile (273)

The title compound was prepared using the method of example 270, starting with 2-(2-chloro-4-nitro-phenylsulfanyl)-benzothiazole-6-carbonitrile (261) (1.6 g, 4.6 mmol), tin chloride dihydrate (Aldrich, 5.21 g, 23.1 mmol). Compound 273 (1.36 g, 93%) was obtained as a yellowish solid. MS (M+H) 318.

EXAMPLE 274

2-(4-Amino-2,6-dichloro-phenylsulfanyl)-benzothiazole-5-carbonitrile

(274)

The title compound was prepared using the method of example 270, starting with 2-(2,6-dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carbonitrile (262) (1.9 g, 4.97 mmol), tin chloride dihydrate (Aldrich, 5.62 g, 24.9 mmol). Compound 274 (1.40 g, 80%) was obtained as a yellowish solid.

¹H NMR (DMSO-d₆) δ 8.35 (d, J = 1.4 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.73 (dd, J = 8.4, 1.5 Hz, 1H), 6.88 (s, 2H), 6.50 (s, 2H). MS (M+H) 352.

EXAMPLE 275

2-(4-Amino-2-chloro-phenylsulfanyl)-benzothiazole-5-carbonitrile

(275)

The title compound was prepared using the method of example 270,
5 starting with 2-(2-chloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carbonitrile (**263**) (1.59 g, 4.58 mmol), tin chloride dihydrate (Aldrich, 5.18 g, 22.9 mmol). Compound **275** (1.35 g, 93%) was obtained as a yellowish solid.

¹H NMR (DMSO-d₆) δ 8.32 (d, J = 1.4 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H),
7.71 (dd, J = 8.3, 1.5 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.65 (dd,
10 J = 8.4, 2.4 Hz, 1H). MS (M+H) 318.

EXAMPLE 276

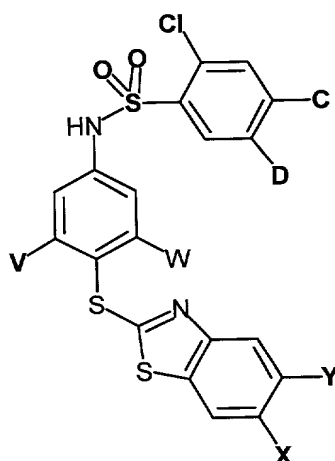
1-[5-Amino-3-chloro-2-(5-methyl-benzothiazol-2-ylsulfanyl)-phenyl]- ethanone (276)

15 To a solution of 1-[3-chloro-5-nitro-2-(5-methyl-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone (**264**) (3.87 g, 10.2 mmol) in 2:2:1 of EtOH/THF/H₂O, was added ammonium chloride (Aldrich 2.74 g, 51.2 mmol) and iron powder (Aldrich, 2.87 g, 51.2 mmol). The mixture was refluxed for 3 hours. The mixture was filtered through Celite pad while it was hot, washed the Celite pad with EtOAc. The filtrate was diluted
20 with saturated aqueous NaHCO₃ solution and was extracted 3x with EtOAc (150 mL). The organic layers were combined and washed twice with a brine solution (100 mL), dried over Na₂SO₄, and concentrated under vacuum. The crude solid was chromatographed (0-15% EtOAc in CH₂Cl₂) to yield 2.42 g (68%) of compound **276** as a pale yellow solid.

25 ¹H NMR (DMSO-d₆) δ 8.10 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 1.1 Hz, 1H), 7.16 (dd, J = 8.1, 1.2 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.69 (d, J = 2.5 Hz, 1H), 6.38 (s, 2H), 2.46 (s, 3H), 2.40 (s, 3H). MS (M+H) 349.

Examples 277-307: The compounds illustrated in Table 32 were prepared by sulfonylation of the anilines of Table 31 by the method of Example 277
30 unless otherwise specified.

Table 32



Example									
	#	C	D	V	W	X	Y	MS(M-H)	Yield
5	277	CF ₃	H	COMe	Cl	H	Cl	609	72%
	278	Cl	H	COMe	Cl	H	Cl	575	39%
	279	Cl	Me	COMe	Cl	H	Cl	589	73%
	280	Cl	H	H	Cl	H	CF ₃	567	68%
	281	CF ₃	H	H	Cl	H	CF ₃	601	70%
10	282	Cl	H	H	Cl	H	CO ₂ Me	557	68%
	283	Cl	H	Cl	Cl	H	CO ₂ Me	557	68%
	284	CF ₃	H	H	Cl	CONH ₂	H	576	14%
	285	CF ₃	H	Cl	Cl	CONH ₂	H	610	55%
	286	CF ₃	H	H	Cl	CN ₄ H	H	601	67%
15	287	CF ₃	H	Cl	Cl	CN ₄ H	H	635	65%
	288	CF ₃	H	H	OMe	H	Cl	563	72%
	289	Cl	H	Cl	Cl	H	CF ₃	601	61%
	290	CF ₃	H	Cl	Cl	H	CF ₃	635	76%
	291	Cl	H	COMe	Cl	H	CF ₃	609	32%
20	292	CF ₃	H	COMe	Cl	H	CF ₃	643	29%
	293	Cl	H	Cl	Cl	CN	H	558	71%
	294	CF ₃	H	Cl	Cl	CN	H	592	83%
	295	Cl	H	H	Cl	CN	H	524	88%
	296	CF ₃	H	H	Cl	CN	H	558	64%
25	297	Cl	H	Cl	Cl	H	CN	558	66%

	298	CF ₃	H	Cl	Cl	H	CN	592	72%
	299	Cl	H	H	Cl	H	CN	524	58%
	300	CF ₃	H	H	Cl	H	CN	558	58%
	301	Cl	H	Cl	Cl	H	CN ₄ H	601	77%
5	302	CF ₃	H	Cl	Cl	H	CN ₄ H	635	82%
	303	Cl	H	Cl	Cl	H	CONH ₂	601	77%
	304	Cl	H	H	Cl	H	CN ₄ H	567	78%
	305	CF ₃	H	H	Cl	H	CN ₄ H	601	83%
	306	CF ₃	H	COMe	Cl	H	Me	589	73%
10	307	Cl	Me	COMe	Cl	H	Me	569	74%

EXAMPLE 277

N-[3-Acetyl-5-chloro-4-(5-chloro-benzothiazol-2-ylsulfanyl)-phenyl]-2-chloro-4-trifluoromethyl-benzenesulfonamide (277)

15 To a 1M solution of 1-[5-Amino-3-chloro-2-(5-chloro-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone, (265) (4.12 g, 11.19 mmol) in pyridine, obtained from Aldrich, was added 2-chloro-4-trifluoromethyl-benzenesulfonyl chloride (3.75 g, 13.43 mmol) and heated to 90 °C for 1.5 hours. The crude reaction mixture was concentrated under vacuum, partitioned between 2M aqueous HCl (100 mL) and EtOAc (100 mL), and
20 extracted 3 times with EtOAc (100 mL). The combined organic layers were washed twice with saturated aqueous brine (100 mL), dried over Na₂SO₄, concentrated under vacuum, purified by column chromatography (0-5% Et₂O in CH₂Cl₂), and triturated with CH₂Cl₂/hexane mixture with 0.5 mL of MeOH added to yield compound 277 (4.9 g, 72%) as an off white solid.

25 ¹H NMR (400MHz, DMSO-d₆) δ 11.9 (s, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.23 (s, 1H), 8.01 (bd, J = 7.2 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.9 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.6, 2.1 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 2.45 (s, 3H). MS (EI): m/z 609 (38, M-H), 610 (10, M-H), 611 (50, M-H), 612 (12, M-H), 613 (20, M-H), 614 (5, M-H), 615 (3, M-H).

30

EXAMPLE 278

N-[3-Acetyl-5-chloro-4-(5-chloro-benzothiazol-2-ylsulfanyl)-phenyl]-2,4-dichloro-benzenesulfonamide (278) By the method of example 93.

¹H NMR (DMSO-d₆) δ 11.8 (s, 1H), 8.24 (d, J = 8.6 Hz, 1H), 8.1-7.95 (m, 2 H), 7.91 (d, J = 2.0 Hz, 1H), 7.71 (dd, J = 8.6, 2.1 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.6, 2.1 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 2.45 (s, 3H). MS (M-H) 575.

5

EXAMPLE 279

N-[3-Acetyl-5-chloro-4-(5-chloro-benzothiazol-2-ylsulfanyl)-phenyl]-2,4-dichloro-5-methyl-benzenesulfonamide(279)

¹H NMR (DMSO-d₆) δ 11.8 (s, 1H), 8.3 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.93-7.9 (m, 2H), 7.46 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.6, 2.1 Hz, 1H), 7.3 (d, J = 2.4 Hz, 1H), 2.45 (s, 3H), 2.4 (s, 3H). MS (M-H) 589.

10

EXAMPLE 280

2,4-Dichloro-N-[3-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (280)

¹H NMR (400MHz, DMSO-d₆) δ 11.6 (s, 1 H), 8.23-8.16 (m, 3 H), 7.96 (bs, 1 H), 7.88 (bd, J = 8.6 Hz, 1H), 7.75-7.67 (m, 2 H), 7.4 (bs, 1H), 7.23 (bd, J = 10.7 Hz, 1 H). MS M-H) 567.

15

EXAMPLE 281

2-Chloro-N-[3-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (281)

20

¹H NMR (400MHz, DMSO-d₆) δ 11.8 (s, 1 H), 8.4 (d, J = 8.3 Hz, 1 H), 8.23 (bs, 1 H), 7.98-7.94 (m, 2 H), 8.03 (bd, J = 8.4 Hz, 1 H), 7.9 (d, J = 8.6 Hz, 1H), 7.69 (bd, J = 10.1 Hz, 1 H), 7.44 (d, J = 2.4 Hz, 1 H), 7.25 (dd, J = 8.5, 2.4 Hz, 1 H). MS (M-H) 601.

25

EXAMPLE 282

2-[2-Chloro-4-(2,4-dichloro-benzenesulfonylamino)-phenylsulfanyl]-benzothiazole-5-carboxylic acid methyl ester(282)

30

¹H NMR (DMSO-d₆) δ 11.5 (s, 1H), 8.32 (d, J = 1.5 Hz, 1H), 8.19 (d, J = 8.6 Hz, 1 H), 8.08 (d, = 8.4 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 9.1, 1.6 Hz, 1 H), 7.88 (d, J = 8.6 Hz, 1H), 7.73 (dd, J = 8.6, 2.1 Hz, 1H), 7.4 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 8.2, 2.0 Hz, 1 H), 3.9 (s, 3H). MS (M-H) 557.

EXAMPLE 283

2-[2,6-Dichloro-4-(2,4-dichloro-benzenesulfonylamino)-phenylsulfanyl]-benzothiazole-5-carboxylic acid methyl ester(283) By the method of example 93.

^1H NMR (DMSO- d_6) δ 11.9 (s, 1H), 8.32 (d, J = 0.9 Hz, 1H), 8.22 (d, J = 8.6 Hz, 1 H), 8.09 (d, J = 8.4 Hz, 1H), 8.0 (d, J = 1.9 Hz, 1H), 7.92 (dd, J = 8.4, 1.6 Hz, 1 H), 7.75 (dd, J = 8.6, 2.1 Hz, 1H), 7.4 (s, 2H), 3.9 (s, 3H). MS (M-H) 591.

EXAMPLE 284

2-[2-Chloro-4-(2-chloro-4-trifluoromethyl-benzenesulfonylamino)-phenylsulfanyl]-benzothiazole-6-carboxylic acid amide (284)

2-[2-Chloro-4-(2-chloro-4-trifluoromethyl-benzenesulfonylamino)-phenylsulfanyl]-benzothiazole-6-carboxylic acid amide (284) was prepared (14%) from 2-chloro-N-[3-chloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (296) by the method of example 303.

^1H NMR (DMSO- d_6) δ 11.8 (s, 1H), 8.42 (d, J = 1.3 Hz, 1H), 8.38 (d, J = 8.5 Hz, 1 H), 8.21 (bs, 1H), 8.05-7.99 (m, 2H), 7.94 (dd, J = 8.6, 1.5 Hz, 1 H), 7.89-7.83 (m, 2H), 7.45 (s, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.24 (dd, J = 8.5, 2.1 Hz, 1H). MS (M-H) 576.

EXAMPLE 285

2-[2,6-Dichloro-4-(2-chloro-4-trifluoromethyl-benzensulfonylamino)-phenylsulfanyl]-benzothiazole-6-carboxylic acid amide (285)

2-[2,6-Dichloro-4-(2-chloro-4-trifluoromethyl-benzensulfonylamino)-phenylsulfanyl]-benzothiazole-6-carboxylic acid amide (285) was prepared (55%) from 2-chloro-N-[3,5-dichloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (294), by the method of example 303.

^1H NMR (DMSO- d_6) δ 12.0 (bs, 1H), 8.48-8.4 (m, 2H), 8.23 (bs, 1H), 8.05-8.0 (m, 2H), 7.95 (dd, J = 8.5, 1.7 Hz, 1 H), 7.85 (d, J = 8.5 Hz, 1H), 7.48 (s, 1H), 7.4 (s, 2H). MS (M-H) 610.

EXAMPLE 286

2-Chloro-N-{3-chloro-4-[6-(1H-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide

2-Chloro-N-{3-chloro-4-[6-(1H-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (286) was prepared (67%) from 2-chloro-N-[3-chloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (296), by the method of example 301.

¹H NMR (DMSO-d₆) δ 8.62 (bs, 1H), 8.36 (d, J = 8.5 Hz, 1H), 8.19 (bs, 1H), 8.08 (d, J = 8.1 Hz, 1H), 8.04-7.95 (m, 2H), 7.84 (d, J = 8.6 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.2 (dd, J = 7.9, 1.8 Hz, 1H). MS (M-H) 601.

EXAMPLE 287

2-Chloro-N-{3,5-dichloro-4-[6-(1H-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (287)

2-Chloro-N-{3,5-dichloro-4-[6-(1H-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (287) was prepared (65%) from 2-chloro-N-[3,5-dichloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (294) by the method of example 301.

¹H NMR (DMSO-d₆) δ 8.65 (bs, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.24 (bs, 1H), 8.09 (d, J = 8.6 Hz, 1H), 8.06-7.98 (m, 2H), 7.4 (bs, 2H). MS (M-H) 635.

EXAMPLE 288

2-Chloro-N-[4-(5-chloro-benzothiazol-2-ylsulfanyl)-3-methoxy-phenyl]-4-trifluoromethyl-benzenesulfonamide (288) By the method of example 93.

¹H NMR (DMSO-d₆) δ 11.5 (s, 1H), 8.4 (d, J = 8.3 Hz, 1H), 8.2 (bs, 1H), 8.01 (d, J = 8.3, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 8.6, 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 6.83 (dd, J = 8.4, 2.1 Hz, 1H), 3.8 (s, 3H). MS (M-H) 563.

EXAMPLE 289

2,4-Dichloro-*N*-[3,5-dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (289)

¹H NMR (DMSO-d₆) δ 11.90 (s, 1H), 8.25-8.15 (m, 3H), 7.98 (d, J = 2.0 Hz, 1H), 7.76-7.67 (m, 2H), 7.38 (s, 2H). MS (M-H) 601

EXAMPLE 290

2-Chloro-*N*-[3,5-dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (290)

¹H NMR (DMSO-d₆) δ 11.90 (br s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.26-8.15 (m, 3H), 8.03 (dd, J = 8.4, 1.7 Hz, 1H), 7.68 (dd, J = 8.6, 1.6 Hz, 1H), 7.40 (s, 2H). MS (M-H) 635.

EXAMPLE 291

***N*-[3-Acetyl-5-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-2,4-dichloro-benzenesulfonamide (291)**

¹H NMR (DMSO-d₆) δ 11.80 (br s, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.22-8.15 (m, 2H), 7.97 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 8.6, 2.1 Hz, 1H), 7.69 (dd, J = 8.6, 1.6 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 2.47 (s, 3H). MS (M-H) 609.

EXAMPLE 292

***N*-[3-Acetyl-5-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-2-chloro-4-trifluoromethyl-benzenesulfonamide (292)**

¹H NMR (DMSO-d₆) δ 11.90 (br s, 1H), 8.42 (d, J = 8.1 Hz, 1H), 8.23-8.17 (m, 3H), 8.01 (dd, J = 8.5, 1.4 Hz, 1H), 7.65 (dd, J = 8.5, 1.5 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 2.48 (s, 3H). MS (M-H) 643.

EXAMPLE 293

2,4-Dichloro-*N*-[3,5-dichloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (293)

¹H NMR (DMSO-d₆) δ 11.90 (br s, 1H), 8.49 (d, J = 1.1 Hz, 1H), 8.23 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.86 (dd, J = 8.5, 1.6 Hz, 1H), 7.74 (dd, J = 8.6, 2.0 Hz, 1H), 7.38 (s, 2H). MS (M-H) 558.

EXAMPLE 294

2-Chloro-*N*-[3,5-dichloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (294)

¹H NMR (DMSO-d₆) δ 11.90 (br s, 1H), 8.49 (d, J = 1.5 Hz, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.24 (br s, 1H), 8.03 (dd, J = 8.2, 1.0 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.87 (dd, J = 8.5, 1.7 Hz, 1H), 7.40 (s, 2H). MS (M-H) 592.

EXAMPLE 295

2,4-Dichloro-*N*-[3-chloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (295)

¹H NMR (DMSO-d₆) δ 11.60 (br s, 1H), 8.49 (d, J = 1.8 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.00-7.94 (m, 2H), 7.90-7.84 (m, 2H), 7.72 (dd, J = 8.6, 2.0 Hz, 1H), 7.41 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.5, 2.4 Hz, 1H). MS (M-H) 524.

EXAMPLE 296

2-Chloro-*N*-[3-chloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (296)

¹H NMR (DMSO-d₆) δ 11.78 (br s, 1H), 8.48 (br s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.22 (br s, 1H), 8.02 (br d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.86 (dd, J = 8.5, 1.5 Hz, 1H), 7.43 (d, J = 2.3 Hz, 1H), 7.25 (dd, J = 8.5, 2.4 Hz, 1H). MS (M-H) 558.

EXAMPLE 297

2,4-Dichloro-*N*-[3,5-dichloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (297)

¹H NMR (DMSO-d₆) δ 11.90 (br s, 1H), 8.36 (d, J = 1.1 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 8.5, 1.5 Hz, 1H), 7.73 (dd, J = 8.4, 2.0 Hz, 1H), 7.38 (s, 2H). MS (M-H) 558.

EXAMPLE 298

2-Chloro-*N*-[3,5-dichloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (298)

¹H NMR (DMSO-d₆) δ 11.98 (br s, 1H), 8.43 (d, J = 8.3 Hz, 1H), 8.35 (d, J = 1.5 Hz, 1H), 8.23 (br s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.03 (dd, J = 8.4, 1.0 Hz, 1H), 7.76 (dd, J = 8.4, 1.4 Hz, 1H), 7.40 (s, 2H). MS (M-H) 592.

EXAMPLE 299

2,4-Dichloro-*N*-[3-chloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide

¹H NMR (DMSO-d₆) δ 11.60 (br s, 1H), 8.36 (d, J = 1.5 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.75 (dd, J = 8.4, 1.5 Hz, 1H), 7.72 (dd, J = 8.5, 2.0 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 8.5, 2.4 Hz, 1H). MS (M-H) 524.

EXAMPLE 300

2-Chloro-*N*-[3-chloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (300)

¹H NMR (DMSO-d₆) δ 11.70 (br s, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 1.4 Hz, 1H), 8.21 (br s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.03 (dd, J = 8.5, 1.5 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.75 (dd, J = 8.4, 1.6 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 8.5, 2.4 Hz, 1H). MS (M-H) 558.

EXAMPLE 301

2,4-Dichloro-*N*-{3,5-dichloro-4-[5-(1*H*-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-benzenesulfonamide (301)

To a solution of 2,4-dichloro-*N*-[3,5-dichloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (**297**) (250 mg, 0.45 mmol) in toluene (5 mL), was added azidotrimethylsilane (Aldrich, 0.12 mL, 0.90 mmol) and dibutyltin oxide (Aldrich, 11 mg, 0.045 mmol). The resulting mixture was heated at 90 °C overnight (15 hours). A 1M aqueous solution of HCl (50 mL) and ice was added and the crude reaction mixture was extracted 3x with EtOAc (50 mL). The organic layers were combined and washed twice with a brine solution (100 mL), dried over Na₂SO₄, and concentrated under vacuum. The crude solid was chromatographed (20% EtOAc in CH₂Cl₂, then 10% MeOH in CH₂Cl₂) to yield 209 mg (77%) of product as a white solid.

¹H NMR (DMSO-*d*₆) δ 8.44 (d, *J* = 1.7 Hz, 1H), 8.21 (d, *J* = 8.6 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.01 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.72 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.38 (s, 2H). MS (M-H) 601.

EXAMPLE 302

2-Chloro-*N*-{3,5-dichloro-4-[5-(1*H*-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (302)

The title compound was prepared by the method of example 301.

¹H NMR (DMSO-*d*₆) δ 8.44 (d, *J* = 1.5 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 1.3 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.02 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.40 (s, 2H). MS (M-H) 635.

EXAMPLE 303

2-[2,6-Dichloro-4-(2,4-dichloro-benzenesulfonylamino)-phenylsulfanyl]-benzothiazole-5-carboxylic acid amide (303)

To a solution of 2,4-dichloro-*N*-[3,5-dichloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (**297**) (250 mg, 0.45 mmol) in *tert*-butanol (10 mL), was added KOH (EM Science Product, 126 mg, 2.25 mmol). The resulting mixture was refluxed for 1 hour. After cooling to room temperature, a 1M aqueous solution of HCl (50 mL) was added and the crude reaction mixture was extracted 3x with EtOAc (50 mL). The organic layers were combined and washed twice with a brine solution (100

mL), dried over Na₂SO₄, and concentrated under vacuum. The crude solid was chromatographed (20% EtOAc in CH₂Cl₂, then 10% MeOH in CH₂Cl₂) to yield 207 mg (80%) of compound **303** as a white solid.

¹H NMR (DMSO-d₆) δ 11.80 (s, 1H), 8.33 (br s, 1H), 8.22 (dd, J = 8.5, 1.9 Hz, 1H), 8.08 (br s, 1H), 8.03-7.96 (m, 2H), 7.85 (m, 1H), 7.74 (m, 1H), 7.47 (br s, 1H), 7.38 (s, 2H). MS (M-H) 578.

EXAMPLE 304

2,4-Dichloro-N-{3-chloro-4-[5-(1H-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-benzenesulfonamide (304) The title compound was prepared by the method of example 301.

¹H NMR (DMSO-d₆) δ 8.44 (d, J = 1.5 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.01 (dd, J = 8.4, 1.6 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.71 (dd, J = 8.6, 2.1 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 8.6, 2.4 Hz, 1H). MS (M-H) 567.

EXAMPLE 305

2-Chloro-N-{3-chloro-4-[5-(1H-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (305).

The title compound was prepared by the method of example 301.

¹H NMR (DMSO-d₆) δ 8.43 (d, J = 1.5 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 1.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.03-7.96 (m, 2H), 7.85 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.20 (dd, J = 8.6, 2.4 Hz, 1H). MS (M-H) 601.

EXAMPLE 306

N-[3-Acetyl-5-chloro-4-(5-methyl-benzothiazol-2-ylsulfanyl)-phenyl]-2-chloro-4-trifluoromethyl-benzenesulfonamide (306).

¹H NMR (DMSO-d₆) δ 11.90 (br s, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.23 (d, J = 1.2 Hz, 1H), 8.01 (dd, J = 8.4, 1.1 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.19 (dd, J = 8.5, 1.2 Hz, 1H), 2.47 (s, 3H), 2.40 (s, 3H). MS (M-H) 589.

EXAMPLE 307

***N*-[3-Acetyl-5-chloro-4-(5-methyl-benzothiazol-2-ylsulfanyl)-phenyl]-2,4-dichloro-5-methyl-benzenesulfonamide (307)**

¹H NMR (DMSO-d₆) δ 11.70 (br s, 1H), 8.28 (s, 1H), 7.92 (s, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.64 (s, 1H), 7.45 (d, J = 2.3 Hz, 1H), 7.29 (d, J = 2.3 Hz, 1H), 7.19 (dd, J = 8.2, 1.5 Hz, 1H), 2.48-2.38 (m, 9H). MS (M-H) 569.

EXAMPLE 308

3-Hydroxy-6-methylquinoline (308)

A solution of 3-Amino-6-methylquinoline [(1.21g, 7.65mmol), prepared according to J.Chem.Soc.2024-2027(1948) Morley, J. S.; Simpson, J. C. E.] in 6N H₂SO₄ (25ml) was cooled in an ice bath. To the solution NaNO₂ (560mg, 8.10mmol) in water (2ml) was added and stirred for 30min at 0 degrees. Separately 5% H₂SO₄ was refluxed and above Diazo reaction mixture was added to this refluxing solution. After 30min the reaction mixture was cooled to room temperature, and was neutralized by 6N NaOH. The resulting insoluble material was collected by filtration. This solid was recrystallized by CHCl₃/AcOEt to afford compound (308) (348mg, 29%).

¹H NMR (300MHz,DMSO-d₆) δ 7.34 (1H, dd, J=1.9, 8.6Hz), 7.42(1H, d, J=2.8Hz), 7.55 (1H, s), 7.79 (1H, d, J=8.6Hz), 8.50 (1H, d, J=2.8Hz).

EXAMPLE 309

3-(2,6-Dichloro-4-nitro-phenoxy)-6-methyl-quinoline (309)

To a solution of 3-Hydroxy-6-methylquinoline (308) (348mg, 2.19mmol) in DMF (3.5ml), was added NaH (60% oil suspension, 90mg, 2.25mmol) in one portion at room temperature. After 5min 3,4,5-Trichloronitrobenzene (509mg, 2.25mmol) in DMF (2ml) was added and the reaction mixture was heated at 50 degrees with stirring for 2hr. After cooling to room temperature. Ice/water was added to the reaction mixture, which was then acidified with 2N HCl and extracted twice with AcOEt. Organic layer was washed with Brine, dried over anhydrous MgSO₄, and concentrated. Crude residue was purified by column chromatography (Hexane/AcOEt=4/1, 80g of silica gel) to afford compound 309 (510mg, 67%).

¹H NMR (300MHz,DMSO-d₆) δ 7.52-7.57(2H,m), 7.61 (1H, s), 7.94(1H, d, J=8.6Hz), 8.63 (2H, s), 8.86 (1H, d, J=2.9Hz).

EXAMPLE 310

3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-6-carboxylic acid (310).

A solution of 3-(2,6-Dichloro-4-nitro-phenoxy)-6-methyl-quinoline(309)
5 (510mg, 1.46mmol) and chromium (VI) oxide (292mg, 2.92mmol) in c H₂SO₄/ H₂O
=2.4ml/4.7ml was heated at 100 degrees while three 292mg portions of chromic
anhydride were added eight hour intervals. After 32hr heating was stopped and allowed
to stand for over night. Insoluble material was collected by filtration, and this solid was
washed with water twice to afford compound (310)(443mg, 80%).

10 ¹H NMR (300MHz,DMSO-d₆) δ 7.94 (1H, d, J=3.0Hz), 8.14(2H, s), 8.56
(1H, s), 8.65 (2H, s), 9.09 (1H, d, J=3.0Hz).

EXAMPLE 311

3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-6-carboxylic acid methyl 15 ester (311)

To a solution of 3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-6-carboxylic
acid (310) (443mg, 0.93mmol) in dry THF (20ml) was added CH₂N₂ in Et₂O solution
[Prepared from Nitrosomethylurea (1.65g) and 50%KOH (5ml)]. This mixture was
stirred at room temperature for 1hr. AcOH (1ml) was added to the reaction mixture,
20 which was then concentrated. Sat NaHCO₃ was added to the residue, which was
extracted twice with AcOEt. Organic layer was washed by Brine, dried over anhydrous
MgSO₄, and concentrated to afford compound 311 (415mg).

¹H NMR (300MHz,DMSO-d₆) δ 3.89 (3H, s), 5.75(2H, br s), 6.76 (2H, s),
7.73 (1H, d, J=2.9Hz), 8.09 (2H, s), 8.67 (1H, s), 8.94 (1H, d, J=2.9Hz).

25

EXAMPLE 312

3-(4-Amino-2, 6-dichloro-phenoxy)-quinoline-6-carboxylic acid methyl ester (312)

To a solution of 3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-6-carboxylic
30 acid methyl ester (311) (0.93mmol) and NH₄Cl (283mg, 5.3mmol) in EtOH/THF/water
(8ml/16ml/1ml)was added Iron powder (296mg, 5.3mmol). The reaction mixture was
refluxed for 4hr. Insoluble materials were removed by Celite pad, which was washed by
THF, acetone and then EtOH. The filtrate was concentrated, and sat NaHCO₃ was added

and extracted twice with AcOEt. Organic layer was washed by brine, dried over anhydrous MgSO₄, and concentrated to afford compound **312** (372mg, over weight).

¹H NMR (300MHz, DMSO-d₆) δ 3.89 (3H, s), 5.75(2H, s), 6.76 (2H, s), 7.73 (1H, d, J=2.9Hz), 8.09 (2H, s), 8.67 (1H, s), 8.94 (1H, d, J=2.9Hz).

5

EXAMPLE 313

3-Hydroxy-8-quinolinecarboxylic acid methyl ester (313)

To the mixture of 8-Quinoline carboxylic acid (500mg, 2.89mmol) in THF (80ml) was added CH₂N₂ in Et₂O sol. [Prepared from Nitrosomethylurea (1.65g) and 10 50%KOH (5ml)] at room temperature. The reaction mixture was stirred for 12 hr and then concentrated to give the intermediate ester.

¹H NMR (300MHz, DMSO-d₆) δ 3.92 (3H, s), 7.60-7.70 (2H, m), 7.93-7.96(1H, m), 8.14-8.17 (1H, m), 8.44-8.48(1H, m), 8.97-8.99(1H, m)

To a solution of the intermediate 8-Quinolinecarboxylic acid methyl ester 15 (2.89mmol) in AcOH (4ml) was added 30% H₂O₂ (0.6ml). The reaction mixture was heated at 85 degrees for 7.5hr. The reaction mixture was treated with sat NaHCO₃, and extracted six times with CHCl₃. Organic layer was dried over anhydrous MgSO₄, and concentrated. Crude residue was triturated with CHCl₃/Toluene to provide compound **313** (256mg, 44%, in 2 steps).

20 ¹H NMR (300MHz, DMSO-d₆) δ 3.89 (3H, s), 7.52(1H, d, J=6.9Hz), 7.57 (1H, d, J=1.5Hz), 7.66 (1H, dd, J=1.5, 6.9Hz), 7.95 (1H, dd, J=1.5, 8.1Hz), 8.63 (1H, d, J=2.7Hz), 10.5 (1H, br s).

EXAMPLE 314

3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-8-carboxylic acid methyl ester (314)

To a solution of 3-Hydroxy-8-quinolinecarboxylic acid methyl ester (**313**) (256mg, 1.26mmol) and 3,4,5-Trichloronitrobenzene (294mg, 1.30mmol) in Acetone (40ml) was added K₂CO₃ (870mg, 6.30mmol). This mixture was refluxed for 3.5hr. The 30 reaction mixture was cooled to room temperature and insoluble materials were removed by Celite filtration. The filtrate was concentrated and the residue was purified by column chromatography. (Hexane/AcOEt=4/1, 80g of silica gel) to afford compound **314**.

^1H NMR (300MHz,DMSO- d_6) δ 3.92 (3H, s), 7.67(1H, dd, $J=7.3\text{Hz}$), 7.79 (1H, d, $J=2.9\text{Hz}$), 7.88 (1H, dd, $J=1.5, 7.3\text{Hz}$), 9.05 (1H, d, $J=2.9\text{Hz}$).

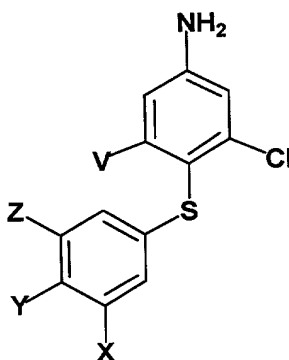
EXAMPLE 315

5 **3-(4-Amino-2, 6-dichloro-phenoxy)-quinoline-8-carboxylic acid methyl ester(315).**

To a solution of 3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-8-carboxylic acid methyl ester (**314**) (1.26mmol) and NH_4Cl (370mg, 6.91mmol) in EtOH/THF/ H_2O =8ml/4ml/2ml was added Iron powder (386mg, 6.91mmol). The reaction mixture
10 was.refluxed for 3.5hr. After cooling to room temperature and insoluble materials were filtered by Celite filtration. The filtrate was concentrated and sat NaHCO_3 was added to the residue, which was extracted twice with AcOEt. Organic layer was washed by Brine, dried over MgSO_4 , and concentrated. Crude residue was purified by column chromatography (Hexane/AcOEt=2/1, 80g of silica gel) to afford compound **315**
15 (543mg).

^1H NMR (300MHz,DMSO- d_6) δ 3.91(3H, s), 5.77(2H, br s), 6.78 (2H, s), 7.50 (1H, d, $J=3.0\text{Hz}$), 7.61 (1H, dd, $J=8.1\text{Hz}$), 7.81 (1H, dd, $J=1.4, 6.4\text{Hz}$), 8.08 (1H, dd, $J=1.4\text{Hz}, 6.4\text{Hz}$), 8.93 (1H, d, $J=3.0\text{Hz}$).

20 **Table 33**



Example

#	V	X	Y	Z
25 316	H	Cl	H	Cl
317	H	F	F	H
318	H	F	H	F

EXAMPLE 316**3-chloro-4- (3,5-dichloro-phenylsulfanyl)-phenylamine (316).**

5 A solution of potassium t-butoxide (1M in THF) (13 ml) was added via syringe to a solution of 3,5 dichlorothiophenol (2.37 g) and 3-chloro-4-fluoro-nitrobenzene (2.3 g) in THF (20 mL). The exothermic reaction was allowed to stir until it cooled to room temperature. It was poured into water. The resulting solid was collected by filtration and rinsed quickly with ether to leave the intermediate nitro compound. (3.5
10 g). This was dissolved in ethyl acetate at reflux. Tin (II) chloride dihydrate (2.3g) was added in portions as a solid and the reflux continued for 2 hr. After cooling, the mixture was diluted in ethyl acetate, quenched with KOH (0.5 N, 500 mL) and extracted with ethyl acetate 3 X. The organic layer was washed with water, dried over magnesium sulfate and concentrated to afford the aniline (316) (2.9 g) as a light tan solid useable in
15 subsequent reactions. Mp 157-160°C.

^1H NMR (DMSO) δ 7.36 (d, J=8.4 Hz, 1H), 7.341 (t, J=2 Hz, 1H), 6.91 (m, 2H), 6.831 (d, J=2.4 Hz, 1H), 6.602 (dd, J=8.4, 2.8 Hz, 1H), 6.01 (br s, 2H).

EXAMPLES 317 AND 318

20 3,4 difluorothiophenol and 3,5-difluorothiophenol were prepared by the method of D.K. Kim et al (J. Med. Chem. 40, 2363-2373 (1997) and converted by the method of example 316 to the corresponding anilines.

EXAMPLE 317**3-chloro-4- (3,5-difluoro-phenylsulfanyl)-phenylamine (317)**

25 ^1H NMR (DMSO) δ 7.361 (d, J=8.4 Hz, 1H), 6.983 (m, 1H), 6.84 (d, J=2.4 Hz, 1H) 6.61 (m, 3H), 6.02 (s, 2H).

EXAMPLE 318**3-chloro-4- (3,4-difluoro-phenylsulfanyl)-phenylamine (318)**

30 ^1H NMR (acetone) δ 7.377 (d, J=8.4 Hz, 1H), 7.258 (dt J=10.4, 8.4 Hz, 1H), 6.97 (m, 1H) 6.94 (m, 2H), 6.714 (dd, 8.4, 2.5 Hz, 1H), 5.42 (s, 2H).

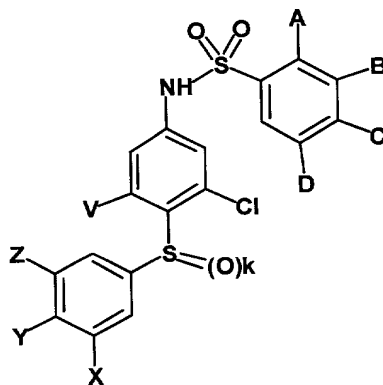
EXAMPLE 319

3,5-Dichloro-4- (3,4-dimethyl-phenylsulfanyl)-phenylamine (319).

A mixture of 3,4-dimethylthiophenol (1.38g, 10mmol), 3,4,5-trichloronitrobenzene 2.49g, 11mmol) and K_2CO_3 (4.15g, 30mmol) in acetone (15ml) was refluxed for 2 hr. After reaction mixture was concentrated, crude product was purified by column chromatography (H/A=9/1, 180g of silica gel) to afford a yellow oil. Unpurified crude 3,5-Dichloro-4- (3,4-dimethyl-phenylsulfanyl)-nitrobenzene was dissolved in CH_2Cl_2 /AcOEt (5ml/20ml). To the solution was added $SnCl_2 \cdot 2H_2O$ (9.03g, 40mmol) and the reaction mixture was stirred at room temperature for 12 hr. 30% NaOH was added to the reaction mixture, which was extracted twice with AcOEt. Organic layer was washed by water, dried over $MgSO_4$ and concentrated to give 2.86g (96% 2 steps) of compound 319 as a white solid.

1H NMR (300MHz, DMSO- d_6) δ 2.14(6H, s), 6.11(2H, br s), 6.66(1H, dd, J=1.8, 8.1Hz), 6.77(2H, s), 6.82(1H, d, J=1.8Hz), 7.02(1H, d, J=8.1Hz).

Table 34



20	EXAMPLE										MS
	#	k	A	B	C	D	V	X	Y	Z	(M-H)
	320	O	Cl	H	Cl	H	H	Cl	H	Cl	509.9
	321	1	Cl	H	Cl	H	H	Cl	H	Cl	525.8
	322	2	Cl	H	Cl	H	H	Cl	H	Cl	541.8
25	323	O	Cl	H	Cl	H	H	F	H	F	478
	324	1	Cl	H	Cl	H	H	F	H	F	
	325	2	Cl	H	Cl	H	H	F	H	F	509.9

	326	O	Cl	H	CF ₃	H	H	F	H	F	512
	327	1	Cl	H	CF ₃	H	H	F	H	F	461
	328	2	Cl	H	CF ₃	H	H	F	H	F	544
	329	O	Cl	H	Cl	Me	H	F	H	F	491.9
5	330	1	Cl	H	Cl	Me	H	F	H	F	
	331	2	Cl	H	Cl	Me	H	F	H	F	523.8
	332	O	Cl	H	Cl	H	H	F	F	H	
	333	1	Cl	H	Cl	H	H	F	F	H	493.9
	334	2	Cl	H	Cl	H	H	F	F	H	509.9
10	335	O	Cl	H	CF ₃	H	H	F	F	H	512
	336	1	Cl	H	CF ₃	H	H	F	F	H	493.9
	337	2	Cl	H	CF ₃	H	H	F	F	H	544
	338	0	Cl	H	CF ₃	H	Cl	Me	Me	H	540

15 EXAMPLES 320-337

The anilines of Table 33 were sulfonylated by the method of example 3 and then oxidized to the corresponding sulfoxide by the method of example 103 or sulfone by the method of example 104 to provide the examples 320-337 illustrated in Table 34.

20

EXAMPLE 324

¹H NMR (DMSO) δ 11.5 (br s, 1H), 8.12 (d, J=8.8 Hz, 1H), 7.88 (d, J=2 Hz, 1H), 7.748 (d, J= 8 Hz, 1H), 7.661 (dd, J=8.8, 2 Hz, 1H), 7.476 (m, 1H), 7.42 (m, 2H), 7.28 (dd, J=8.4, 2 Hz, 1H) 7.17 (br s, 1H).

25

EXAMPLE 330

¹H NMR (acetone) δ 10.1 (br s, 1H), 8.147 (s, 1H), 7.80 (d, 1H), 7.648 (s, 1H), 7.49 (m, 1H), 7.40 (m, 2H), 7.15 (d, 1H), 2.433 (s, 3H).

30

EXAMPLE 332

¹H NMR (acetone) δ 9.80 (br s, 1H), 8.162 (d, J=8.4 Hz, 1H), 7.735 (d, J=2 Hz, 1H), 7.615 (dd, J=8.4, 2.1 Hz, 1H), 7.436 (d, J= 2.2 Hz, 1H), 7.358 (dt, J=10.5,

8.4 Hz, 1H), 7.292 (ddd, 1H), 7.224 (dd, J=8.4, 2.3 Hz, 1H), 7.176 (d, J=8.4 Hz, 1H), 7.16 (m, 1H).

EXAMPLE 338

5 2-Chloro-N-[3,5-dichloro-4-(3,4-dimethyl-phenylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (338)

A solution of aniline 319 (860mg, 2.68mmol) and 3-chloro-4-trifluoromethylbenzene-sulfonylchloride (658mg, 2.68mmol) in pyridine (10ml) was stirred at room temperature for 2-hr. Water was added to the reaction mixture, which was
10 then acidified by 2N HCl. Reaction mixture was extracted twice with AcOEt. Organic layer was washed by Brine, dried over MgSO₄ and concentrated. Crude residue was purified by column chromatography (H/A=4/1, 80g of silica gel) to afford compound 317 (591mg, 41%) as a white solid.

¹H NMR (400MHz,DMSO-d₆) δ 2.11(3H,s), 2.13(3H,s), 6.78(1H,dd, J=2.1,8.3Hz), 6.81(1H,s), 7.01(1H,d, J=8.3Hz), 7.30(2H, s), 7.98(2H,dd, J=2.1,8.3Hz), 8.18(1H,s), 8.35(1H, d, J=8.3Hz), 11.6(1H, br s), mp 156-158 °C. MS (M+H) 540.

EXAMPLE 339

20 3,5-Dichloro-4- (6-methyl-quinolin-3-yloxy)-phenylamine (339)

To a solution of 3-(2,6-Dichloro-4-nitro-phenoxy)-6-methyl-quinoline (309) (1.30g, 3.71mmol) and NH₄Cl (992mg, 18.55mmol) in EtOH/THF/ H₂O =12ml/12ml/3ml, was added Iron Powder (1.04g, 18.55mmol). The mixture was refluxed for 4 hr. Insoluble materials were removed by Celite filtration. The filtrate was concentrated and sat NaHCO₃ was added to the residue, which was then extracted twice
25 with AcOEt. Organic layer was washed with Brine, dried over anhydrous MgSO₄, and concentrated to afford compound 339 (1.18g, 98%).

¹H NMR (300MHz,DMSO-d₆) δ 2.44 (3H, s), 5.75 (2H, br s), 6.77 (2H, s), 7.27 (1H, d, J=2.8Hz), 7.48 (1H, d, J=8.6Hz), 7.67 (1H, s), 7.89 (1H, d, J=8.6Hz), 8.74 (1H, d, J=2.8Hz)

30

EXAMPLE 340

2-Mercapto -4-methyl-benzothiazole (340)

The title compound was prepared using the method of example 239, starting with 2-bromo-4-methyl-phenylamine (Acros) (27.9g), *O*-ethylxanthic acid, potassium salt (Lancaster, 54g) in DMF (250 mL). The mercaptobenzothiazole **340** was obtained as an pale brown solid (27 g). Recrystallization from CHCl_3 gave pinkish white crystals (20g).

^1H NMR (DMSO-d_6) δ 7.499 (br s, 1H), 7.223 (d, $J = 8$ Hz, 1H), 7.198(d, $J=8$ Hz, 1H), 2.342 (s, 3H).

EXAMPLE 341

Compound **341** was prepared by the method of example 84.1 by coupling thiol **340** (9.3g) with 1,2,3,-trichloro-5-nitrobenzene (11.3g) in DMF using NaH as base. Trituration with ether gave **341** (12.4 g) as a yellow solid.

^1H NMR (DMSO-d_6) δ 8.577 (s, 2H), 7.795 (br s, 1H), 7.736 (d, $J = 8.4$ Hz, 1H), 7.303 (d, $J=8.4$ Hz, 1H), 2.405 (s, 3H).

EXAMPLE 342

Reduction of compound **341** (12.4 g) with SnCl_2 by the method of example 32 gave after trituration with methylene chloride, aniline **342** (9 g) as a solid.

^1H NMR (DMSO-d_6) δ 7.709 (br s, 1H), 7.699 (d, $J = 8$ Hz, 1H), 7.262 (d, $J=8$ Hz, 1H), 6.859 (s, 2H), 6.45 (s, 2H), 2.384 (s, 3H).

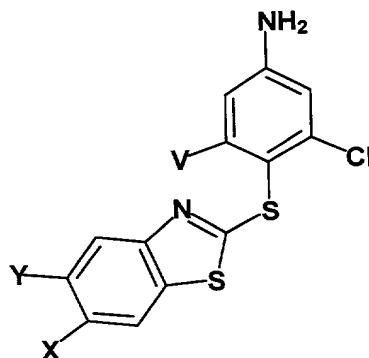
EXAMPLE 344

Compound **344** was prepared by the method of example 84.1 by coupling thiol **245** (2.01 g) with 1,2,3,-trichloro-5-nitrobenzene (2.51g) in DMF using NaH as base. Recrystallization with ether/hexane gave compound **344** (3.2 g) as a yellow solid. Mp 116-118°C.

EXAMPLE 345

Reduction of compound **344** (3.01 g) with SnCl_2 by the method of example 32 gave aniline **345** (2.8 g) as a solid.

^1H NMR (DMSO- d_6) δ 7.772 (d, $J = 8.0$ Hz, 1H), 7.630 (br s, 1H), 7.155 (br d, $J=8$ Hz, 1H), 6.855 (s, 2H), 6.442 (s, 2H), 2.409 (s, 3H). MS (M+H) 341 Anal. calcd.: 49.27% C, 2.95% H, 8.21% N; found. 49.39% C, 3.16 %H, 7.98 %N.



5

Example 342: X=Me, Y=H

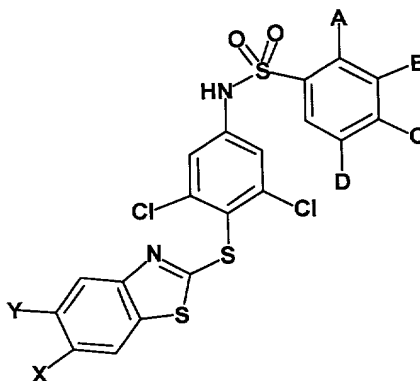
Example 345: X=H, Y=Me

EXAMPLES 346-351

10

Sulfonylation of anilines **342** or **345** by the method of example 3 gave the sulfonamides of Table 35.

Table 35



15 **Example**

#

346

347

348

20 **349**

350

A

B

C

D

X

Y

MS

(M-H)

Cl

H

CF₃

H

Me

H

581

CF₃

H

Cl

H

Me

H

581

Cl

H

Cl

Me

Me

H

561

Cl

H

CF₃

H

H

Me

581

Cl

H

Cl

Me

H

Me

561

EXAMPLE 346

¹H NMR (DMSO-d₆) δ 11.90 (s, 1H), 8.416 (d, J = 8.0 Hz, 1H), 8.228 (br s, 1H), 8.024 (br d, J=8 Hz, 1H), 7.690 (m, 2H), 7.383 (s, 2H), 7.265 (br d, J=8 Hz, 1H), 2.379 (s, 3H). MS (M-H) 580.8.

EXAMPLE 347

¹H NMR(*d*₆-DMSO) δ 11.70-12.00 (1H, broad), 8.22 (1H, d, J = 8.6 Hz), 8.17 (1H, s), 8.08 (1H, d, J = 8.5 Hz), 7.68-7.75 (2H, m), 7.39 (2H, s), 7.28 (1H, d, J = 8.2 Hz), 2.39 (3H, s). MS (M-H) 580.8. mp 227.0 °C. Anal. calcd.: C 43.20, H 2.07, N 4.80; found C 43.23, H 1.97, N 4.91.

EXAMPLE 348

¹H NMR (DMSO-d₆) δ 11.71 (br s, 1H), 8.237 (br s, 1H), 7.915 (s, 1H), 7.708 (s, 1H), 7.698 (d, J=8 Hz, 1H), 7.365 (s, 2H), 7.266 (dd, J=8, 1.6 Hz, 1H), 2.414 (s, 3H), 2.380 (s, 3H). MS (M-H) 560.8.

EXAMPLE 349

¹H NMR (DMSO-d₆) δ 11.94 (br s, 1H), 8.416 (d, J = 8.4 Hz, 1H), 8.231 (d, J=1.6 Hz, 1H), 8.024 (dd, J=8.4, 1.6 Hz, 1H), 7.767 (d, J=8 Hz, 1H), 7.628 (s, 1H), 7.382 (s, 2H), 7.185 (dd, J=8.4, 1.6 Hz, 1H), 2.398 (s, 3H). MS (M-H) 580.8.

EXAMPLE 350

¹H NMR (DMSO-d₆) δ 11.725 (br s, 1H), 8.236 (br s, 1H), 7.918 (s, 1H), 7.785 (d, J=8 Hz, 1H), 7.637 (s, 1H), 7.363 (s, 2H), 7.183 (d, J=8 Hz, 1H), 2.408 (s, 6H). MS (M-H) 560.9.

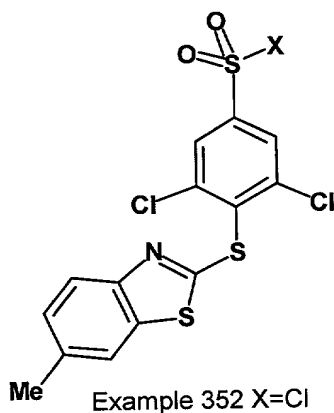
EXAMPLE 351

¹H NMR (*d*₆-DMSO) δ 11.67 (1H, s), 8.12 (1H, d, J = 8.1 Hz), 7.80 (1H, d, J = 8.2 Hz), 7.58-7.68 (2H, m), 7.46 (1H, d, J = 8.1 Hz), 7.35 (2H, s), 7.20 (1H, d, J = 8.2 Hz), 2.40 (6H, s). MS: (M-H) 526.8. mp 112.8 °C. Anal. calcd.: 47.60%C, 2.85% H, 5.29% N; found 47.28%C, 2.98%H, 5.28%N.

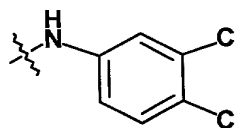
EXAMPLE 352

Aniline **342** was converted according to the method of example 34 to afford the corresponding sulfonyl chloride **352** as a white solid.

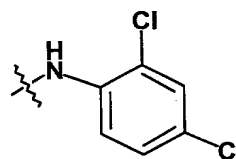
5 ^1H NMR (CDCl_3) δ 8.131 (s, 2H), 7.786 (d, $J = 8.4$ Hz, 1H), 7.567 (br s, 1H), 7.28 (br d, $J = 8$ Hz, 1H), 2.482 (s, 3H).



Example 353 X=



Example 354 X=



EXAMPLE 353

10 Coupling of compound **352** (85 mg) with 3,4-dichloroaniline (42 mg) by the method of example 3 gave the sulfonamide **353** (76 mg) as a white solid.

^1H NMR (d_6 -DMSO) δ 11.01 (1H, s), 8.04 (1H, s), 7.76 (1H, s), 7.72 (1H, d, $J = 8.5$ Hz), 7.62 (1H, d, $J = 8.7$ Hz), 7.34 (1H, s), 7.29 (1H, d, $J = 7.6$ Hz), 7.13-7.23 (1H, m), 2.40 (3H, s). MS (M-H) 546.8. mp 181.0°C. Anal. calcd.: 43.65% C, 2.20% H, 5.09% N; found 43.10% C, 2.21% H, 4.81% N.

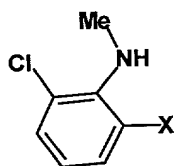
15

EXAMPLE 354

Coupling of compound **352** (85 mg) with 2,4-dichloroaniline (42 mg) by the method of example 3 gave after recrystallization from methanol water, the sulfonamide **354** (38 mg) as a white solid.

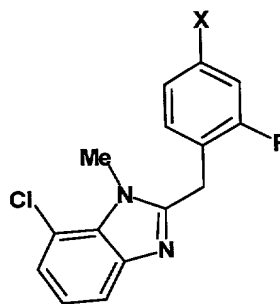
20 ^1H NMR (d_6 -DMSO) δ 10.72 (1H, s), 7.96 (2H, s), 7.79 (1H, s), 7.72-7.77 (2H, m), 7.47 (1H, dd, $J = 8.7, 2.4$ Hz), 7.33 (1H, d, $J = 8.6$ Hz), 7.31 (1H, d, $J = 8.6$ Hz), 2.41 (3H, s). MS (M+H) 548.9. mp 160.7°C. Anal. calcd.: 43.65% C, 2.20% H, 5.09% N; found 43.83% C, 2.19% H, 5.10% N.

25 The following examples illustrate the synthesis of compounds **355-358**.



355 X=NO₂

356 X=NH₂



357 X=NO₂

358 X=NH₂

5

EXAMPLE 355

2,3-dichloronitrobenzene (6.15 g, 32 mmol), methylamine hydrochloride (2.38 g, 35 mmol), triethylamine (9.8 mL, 71 mmol), and DMF (16 mL) were combined in a 100 mL round-bottomed flask and heated to 90°C overnight. The reaction was then cooled to room temperature and dumped over 600 mL of ice-water. The resulting orange solid was collected by filtration and dried at the pump. Recrystallization from hot hexanes yielded 3.2 g (53%) of compound **355** as bright orange crystals.

¹H NMR (d₆-DMSO) δ 7.75 (1H, dd); 7.62 (1H, dd); 6.76 (1H, t); 6.63 (1H, broad s); 2.75 (3H, t).

15

EXAMPLE 356

A round-bottomed flask was charged with 3.8 g (20 mmol) of compound **355**, 22.9 g (102 mmol) of tin dichloride dihydrate, and 125 mL of EtOAc. This was heated to 75°C for 3.0 hours. The reaction was cooled to room temperature, diluted with 300 mL of EtOAc and washed with 250 mL of 2N aqueous KOH solution followed by 200 mL of brine. The organics were dried over sodium sulfate and concentrated to a white amorphous solid **355** (2.9 g, 90%) that was used without further purification (turned brown upon standing in air).

¹H NMR (d₆-DMSO) δ 6.68 (1H, t); 6.56 (2H, m); 4.98 (2H, broad s); 3.76 (1H, broad s); 2.59 (3H, t).

25

EXAMPLE 357

A round-bottomed flask was charged with **356** (1.0 g, 6.4 mmol), 4-nitro-2-fluorophenyl acetic acid (**148**) (1.4 g, 7.0 mmol), and 4N aqueous HCl (13 mL). This was refluxed overnight. The reaction was then cooled and basified with saturated aqueous sodium bicarbonate. The organics were extracted with methylene chloride, dried over Na₂SO₄, and concentrated to a pink solid. This was recrystallized from methylene chloride and hexanes to yield compound **357** (1.4 g, 75%) as fluffy crystals.

¹H NMR (400MHz) (*d*₆-DMSO) δ 8.16 (1H, dd); 8.08 (1H, dd); 7.62 (1H, t); 7.49 (1H, dd); 7.23 (1H, dd); 7.13 (1H, t); 4.48 (2H, s); 4.08 (3H, s).

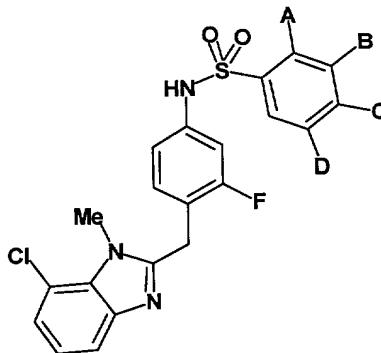
EXAMPLE 358

Nitro compound **357** (1.3 g, 4.0 mmol) was reduced by the method of example 356 to give the aniline **358** (1.0 g, 86%) as off-white crystals. MS (M+H) 290.1.

EXAMPLE 359-361

Aniline **358** was coupled with various sulfonyl chlorides by the method of example 192 to give the sulfonamides illustrated in Table 35

Table 36



EXAMPLE

MS

#	A	B	C	D	yield	(M-H)
359	Cl	H	Cl	H	36%	496
360	H	H	-COMe	H	50%	470
361	Me	H	Cl	Me	60%	
362	Cl	H	Cl	Me	496%	

EXAMPLE 359

¹H NMR (*d*₆-DMSO) δ 11.01 (1H, s); 8.07 (1H, d); 7.87 (1H, d); 7.63 (1H, dd); 7.49 (1H, d); 7.22 (1H, d); 7.15 (2H, m); 6.89 (2H, m); 4.21 (2H, s); 3.99 (3H, s).

5 MS (M-H) 496.0.

EXAMPLE 360

¹H NMR (*d*₆-DMSO) δ 10.78 (1H, s); 8.12 (2H, d); 7.94 (2H, d); 7.51 (1H, d); 7.26 (1H, d); 7.17 (2H, t); 6.97 (2H, m); 4.24 (2H, s); 4.01 (3H, s). MS (M-H) 470.1.

10

EXAMPLE 361

¹H NMR (*d*₆-DMSO) δ 10.75 (1H, s); 7.91 (1H, s); 7.51 (2H, m); 7.26 (1H, d); 7.16 (2H, dd); 6.88 (2H, t); 4.24 (2H, s); 4.01 (3H, s); 2.54 (3H, s); 2.34 (3H, s).

15

EXAMPLE 362

¹H NMR (*d*₆-DMSO) δ 10.97 (1H, s); 8.10 (1H, s); 7.83 (1H, s); 7.52 (1H, d); 7.27 (1H, d); 7.17 (2H, t); 6.94 (2H, m); 4.24 (2H, s); 4.01 (3H, s); 2.38 (3H, s).

EXAMPLE 363

20

This illustrates the preparation of 2,6-dichloro-benzothiazole (**363**).

2-Amino-6-chlorobenzothiazole (15.7g, 85mmol) in H₃PO₄ (85%)(470ml) was heated to 100 degrees and dissolved. Then clear solution was cooled and vigorously stirred by mechanical stirrer. NaNO₂ (17.6g, 255mmol) in water (30ml) was added slowly keeps the temperature below 0 degrees. Separately a solution of
25 CuSO₄·5H₂O(85g), NaCl (107g) in water (350ml) was cooled to -5 degrees and stirred by mechanical stirrer. After Potassium Iodide Starch paper's color was disappeared
Diazonium solution was keeping cold and added slowly to the copper chloride solution with vigorous stirring. The reaction Mixture was allowed to warm to room temperature. After 1-hour water (1L) and ether (1L) were added to the reaction mixture and extracted
30 twice. Organic layer was washed by water and dried over anhydrous MgSO₄ and concentrated. Crude residue was purified by silica gel chromatography (H/A=4/1, 180g of silica gel) to provide title compound **363** (7.46g, 48%).

EXAMPLE 364

This illustrates the preparation of 3,5-dichloro-4- (6-chloro-benzothiazol-2-yloxy)-phenylamine.

To the solution of 4-amino-2, 6-dichloro phenol (6g, 26.5mmol) and 2,6-dichlorobenzothiazole (**363**) (6g, 29.4mmol, 1.1eq) in DMSO (25ml), was added K₂CO₃ (11g, 80mmol, 3.0eq). The mixture was stirred and heated to 160 degree. After 5.5-hr water (20ml) was added to the reaction mixture, which was neutralized with 2N HCl., and was extracted with AcOEt three times. And the organic layer was washed with Brine and was dried over anhydrous MgSO₄, and then concentrated. Crude residue was purified by column chromatography (CHCl₃/Acetone=9/1, 180g of silica gel) to afford 3,5-Dichloro-4- (6-chloro-benzothiazol-2-yloxy)-phenylamine (**364**) as a black solid (4.52g, 49%).

¹H NMR (300MHz,DMSO-d₆) δ 5.86(2H,br s), 6.74(2H,s), 7.48(1H,dd, J=2.1,5.7Hz), 7.70(1H,d, 8.7Hz), 8.10(1H,d, 2.1Hz).

EXAMPLE 365

This illustrates the preparation of 2-Chloro-N- [3,5-dichloro-4- (6-chloro-benzothiazol-2-yloxy)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**365**).

A solution of 3,5-dichloro-4- (6-chloro-benzothiazol-2-yloxy)-phenylamine (**364**) (2.0g, 5.79mmol) and 3-chloro-4-trifluoromethylbenzenesulfonylchloride (1.7g, 6.08mmol) in pyridine (10ml) was stirred at room temperature. After 3-hr water was added to the reaction mixture, which was then acidify by 2N HCl. Reaction mixture was extracted twice with AcOEt. Organic layer was washed by brine, dried over MgSO₄ and concentrated. Crude residue was purified by column chromatography (H/A=4/1, 80g of silica gel) to afford title compound **365** (2.11g, 65%) as a white solid. mp 82-84 °C.

¹H NMR (400MHz,DMSO-d₆) δ 7.32(2H,s), 7.46(1H,dd, J=2.2,8.7Hz), 7.67(1H,d, J=8.7Hz), 8.00(1H,d, 8.0Hz), 8.14(1H,d, J=2.2Hz), 8.20(1H,s), 8.38(1H,d, J=8.3Hz), 11.6(1H,br s). MS (M+H) 586.

EXAMPLE 366

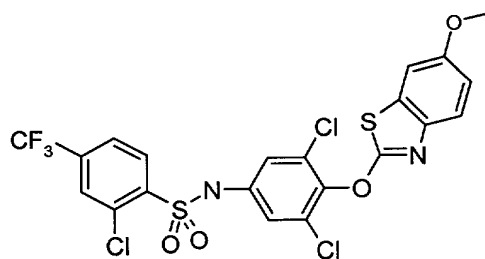
This illustrates the preparation of 2,4-Dichloro-N-[3,5-dichloro-4-(6-chloro-benzothiazol-2-yloxy)-phenyl]benzenesulfonamide (**366**).

A solution of 3,5-dichloro-4-(6-chloro-benzothiazol-2-yloxy)-phenylamine
 (364) (2.0g, 5.79mmol) and 2,4-dichloro benzenesulfonylchloride (1.5g, 6.08mmol) in
 pyridine (10ml) was stirred at room temperature for 12-hr. Water was added to the
 reaction mixture, which was then acidified by 2N HCl. Reaction mixture was extracted
 5 twice with AcOEt. Organic layer was washed by Brine, dried over MgSO₄ and
 concentrated. Crude residue was purified by column chromatography (H/A=4/1, 80g of
 silica gel) to afford title compound (366) (1.49g, 46%) as a white solid. mp 73-75 °C,
¹H NMR (300MHz, DMSO-d₆) δ 7.29 (2H, s), 7.46 (1H, dd, J=2.2, 8.8Hz),
 7.69 (1H, d, J=8.8Hz), 7.71 (1H, dd, J=2.2, 8.4Hz), 7.95 (1H, d, J=2.2Hz), 8.14 (1H, d,
 10 J=2.2Hz), 8.18 (1H, d, J=8.4Hz), 11.5 (1H, br s). MS (M+H) 553.

EXAMPLE 367

This illustrates the preparation of 3,5-Dichloro-4-(6-methoxybenzothiazol-
 2-yloxy)phenylamine (367).
 15 To a solution of 2-chloro-6-methoxybenzothiazole (prepared as described
 by Weinstock et.al., J.Med.Chem.30: p1166 (1987)) and 4-Amino-2,6-dichlorophenol
 1.3g(available from Tokyo Chemical Industry Co., Ltd.) in DMSO(9ml), was added
 K₂CO₃ 3.12g. The mixture was heated at 150 degree for 3hr. The reaction mixture was
 purified by column chromatography(silica gel, AcOEt:Hexane=1:2) to provide the aniline
 20 367 (1.43g, 56%). mp 158-160 °C.

NMR(300MHz/CDCl₃) δ 3.84(3H, s), 3.85(2H, brs), 6.69(2H, s) 6.97(1H,
 dd, J=2.6Hz, J=8.9Hz), 7.18(1H, d, J=2.6Hz), 7.61(1H, d, J=8.9Hz).



EXAMPLE 368

25 This illustrates the preparation of 2-Chloro-N-[3,5-dichloro-4-(6-
 methoxybenzothiol-2-yloxy)-phenyl]-4-trifluoromethyl-benzenesulfonamide (368).
 To a solution of 3,5-dichloro-4-(6-methoxybenzothiazol-2-yloxy)phenylamine (367)
 (1.40g) in pyridine (5ml), was added 2-Chloro-4-trifluorobenzenesulfonamide 1.15g. The

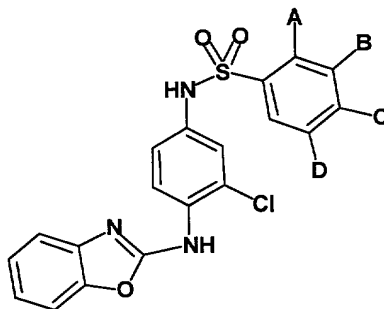
mixture was stirred at room temperature for 2hr. The reaction mixture was purified directly by column chromatography (silica gel, AcOEt:Hexane=1:3). The product was triturated by hexane to give the title compound **368** (1.97g, 82%) as a colorless powder. mp 164-165 °C.

5 NMR (300MHz/DMSO-d₆) δ 3.79(3H, s), 7.00(1H, dd, J=2.9Hz, J=8.8Hz), 7.31(2H, s), 7.55(1H, d, J=8.8Hz), 7.58(1H, d, J=2.9Hz), 8.00(1H, dd, J=1.5Hz, J=8.1Hz), 8.20 (1H, d, J=1.5Hz), 8.37(1H, d, J=8.1Hz), 11.59(1H, brs). MS (M+H) 583.

EXAMPLES 369-370

10 The examples illustrated in Table 37, were prepared from aniline **75** and the corresponding sulfonyl chlorides by the method of procedure 3. The compounds were purified by chromatography on silica gel.

Table 37



15

Example #	MS			
	A	B	C	D (M-H)
369	Cl	H	Cl	H 466
20 370	H	Cl	Cl	H 466
371	Me	H	Cl	Me 460
372	Cl	H	Cl	Me 480

EXAMPLE 369

25 ¹H NMR (d₆-acetone) δ 9.54 (br s, 1H), 8.82 (br s, 1H), 8.446 (d, J=8.8 Hz, 1H), 8.129 (d, J=8.4 Hz, 1H), 7.763 (d, J=2 Hz, 1H), 7.602 (dd, J=8.4, 2 Hz, 1H), 7.428 (m, 2H), 7.327 (dd, J=9.2, 2.4 Hz, 1H), 7.252 (td, J=7.6, 1.2 Hz, 1H), 7.17 (td, J=8, 1.2 Hz, 1H). MS (M-H) 466.0.

EXAMPLE 370

¹H NMR (d6-DMSO) δ 10.643 (br s, 1H), 9.954 (br s, 1H), 7.983 (d, J=2 Hz, 1H), 7.934 (br d, J=8 Hz, 1H), 7.885 (d, J=8.4 Hz, 1H), 7.717 (dd, J=8.4, 2.4 Hz, 1H),
5 7.454 (d, J=8 Hz, 1H), 7.360 (br d, J=7.6 Hz, 1H), 7.226 (d, J=2 Hz, 1H), 7.194 (t, J=8 Hz, 1H), 7.142 (dd, J=8.8, 2 Hz, 1H), 7.106 (t, J=8 Hz, 1H). MS (M-H) 466.0.

EXAMPLE 371

¹H NMR (d6-acetone) δ 9.31 (br s, 1H), 8.80 (br s, 1H), 8.403 (d, J=8 Hz, 1H), 7.928 (s, 1H), 7.45-7.35 (m, 4H), 7.3-7.2 (m, 2H), 7.164 (br t, J=8 Hz, 1H), 2.64 (s, 3H), 2.387 (s, 3H). MS (M-H) 460.0.

EXAMPLE 372

¹H NMR (d6-acetone) δ 9.48 (br s, 1H), 8.82 (br s, 1H), 8.064 (s, 1H),
15 7.707 (s, 1H), 7.45-7.40 (m, 4H), 7.335 (dd, J=8.8, 2HZ, 1H), 7.252 (td, J=7.6, 1.2 Hz, 1H), 7.19 (td, J=8, 1.2 Hz, 1H) 2.425 (s, 3H). MS (M-H) 479.9.

EXAMPLE 373

Using methods similar to Lehmann, *et al.*, *ibid.*, selected compounds
20 exhibited the following IC₅₀ values in a PPAR_γ ligand binding assay utilizing [³H]-BRL 49653 as the radioligand. IC₅₀ values are defined as the concentration of test compounds required to reduce by 50% the specific binding of [³H]-BRL 49653 and are represented by (+) <30 μM; (++) < 10 μM; (+++) < 1 μM.

TABLE 38

Compound	IC ₅₀ (μM)
4.1	+++
16.1	+++
27.3	++
27.5	++
49.1	+++
50.1	+++
72.2	++

72.3	+++
72.4	++
73.4	+++
73.5	+++
73.6	+++
73.7	+++
73.8	+++
73.9	+++
79.5	+++
86	+++
87.3	+++
95	+++
97	+++
108.4	+++
158	+++
160	+++
178	+++
179	+++
219	+++
233	+++
290	+++
292	+++
349	+++
364	++
365	++
368	+++

EXAMPLE 374

Selected compounds were administered to KK-Ay mice as a 0.018% (30 mg/kg) dietary admixture in powdered diet and evaluated for anti-diabetic efficacy as described (T. Shibata, K. Matsui, K. Nagao, H. Shinkai, F. Yonemori and K. Wakitani 1999; *European Journal of Pharmacology* 364:211-219). The change in serum glucose levels compared to untreated control animals is exemplified in Table 39.

TABLE 39

Example #	KKAy Glucose
87.3	++
178	++
179	++
219	+
233	-
364	+
365	++

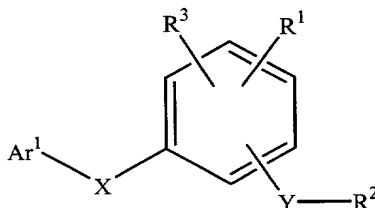
(-) <10%; (+) 10% to 20%; (++) glucose lowering >20%.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although
5 the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

10

WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein

Ar¹ is a substituted or unsubstituted aryl;

X is a divalent linkage selected from the group consisting of (C₁-C₆)alkylene, (C₁-C₆)alkylenoxy, (C₁-C₆)alkylenamino, (C₁-C₆)alkylene-S(O)_k-, -O-, -C(O)-, -N(R¹¹)-, -N(R¹¹)C(O)-, -S(O)_k- and a single bond,

wherein

R¹¹ is a member selected from the group consisting of hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and aryl(C₁-C₄)alkyl; and the subscript k is an integer of from 0 to 2;

Y is a divalent linkage selected from the group consisting of alkylene, -O-, -C(O)-, -N(R¹²)-S(O)_m-, -N(R¹²)-S(O)_m-N(R¹³)-, -N(R¹²)C(O)-, -S(O)_n- and a single bond,

wherein

R¹² and R¹³ are members independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and aryl(C₁-C₄)alkyl; and the subscripts m and n are independently integers of from 0 to 2;

R¹ is a member selected from the group consisting of hydrogen, (C₂-C₈)heteroalkyl, aryl, aryl(C₁-C₄)alkyl, halogen, cyano, nitro, (C₁-C₈)alkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴, -S(O)_q-NR¹⁵R¹⁶, -O-C(O)-OR¹⁷, -O-C(O)-R¹⁷, -O-C(O)-NR¹⁵R¹⁶, -N(R¹⁴)-C(O)-NR¹⁵R¹⁶, -N(R¹⁴)-C(O)-R¹⁷ and -N(R¹⁴)-C(O)-OR¹⁷;

wherein

R¹⁴ is a member selected from the group consisting of hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, aryl and aryl(C₁-C₄)alkyl;

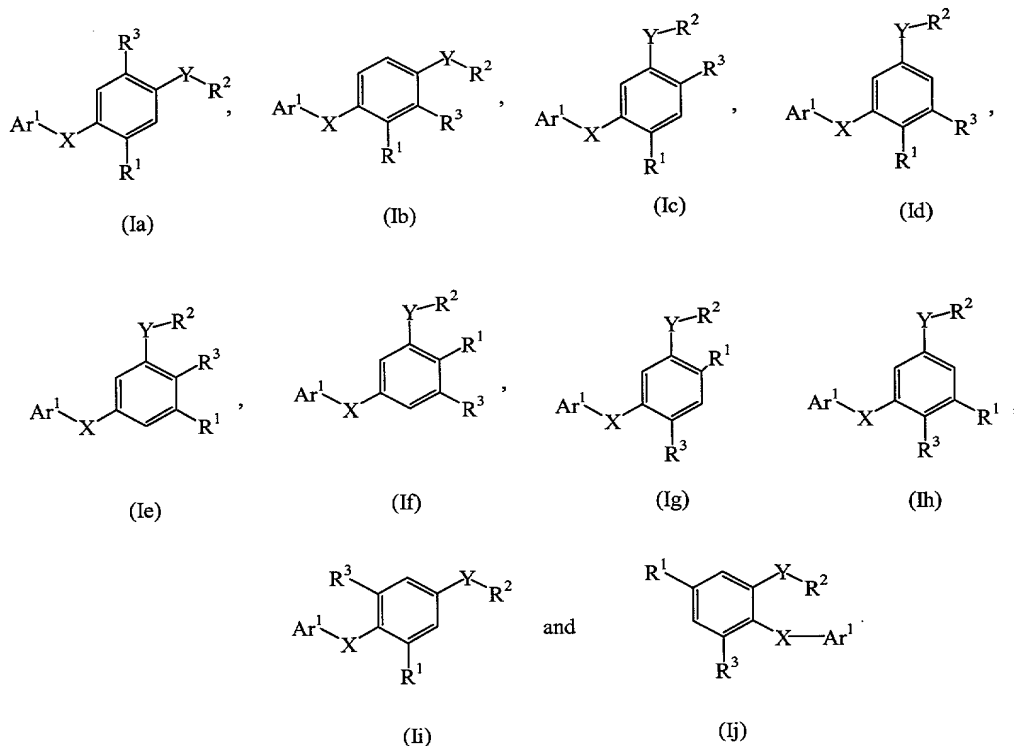
R¹⁵ and R¹⁶ are members independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, aryl, and aryl(C₁-C₄)alkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;

31 R^{17} is a member selected from the group consisting of (C_1-C_8) alkyl, $(C_2-$
 32 $C_8)$ heteroalkyl, aryl and aryl (C_1-C_4) alkyl;
 33 the subscript p is an integer of from 0 to 3; and
 34 the subscript q is an integer of from 1 to 2; and
 35 R^2 is a substituted or unsubstituted aryl; and
 36 R^3 is a member selected from the group consisting of halogen, cyano, nitro and
 37 (C_1-C_8) alkoxy.

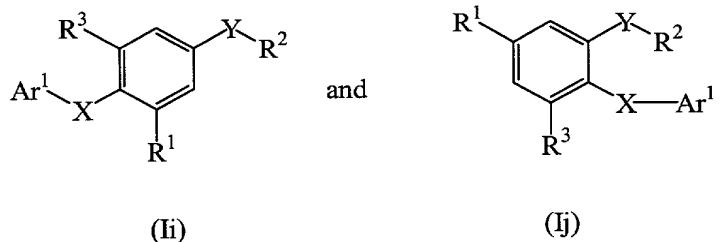
1 2. A compound of claim 1, wherein Ar^1 is a substituted or
 2 unsubstituted aryl selected from the group consisting of pyridyl, phenyl, naphthyl,
 3 isoquinolinyl, benzthiazolyl, benzoxazolyl and benzimidazolyl; with the proviso that
 4 when Ar^1 is substituted or unsubstituted benzthiazolyl, then X is $-S(O)_k-$; and R^2 is a
 5 substituted or unsubstituted aryl selected from the group consisting of phenyl, pyridyl,
 6 naphthyl and pyridazinyl.

1 3. A compound of claim 2, wherein Ar^1 is a substituted or
 2 unsubstituted phenyl group.

1 4. A compound of claim 3, represented by a formula selected from the
 2 group consisting of



1 5. A compound of claim 3, represented by a formula selected from the
2 group consisting of



1 6. A compound of claim 5, wherein

2 X is a divalent linkage selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$,
3 $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{11})-$ and $-\text{S}-$;

4 wherein

5 R^{11} is a member selected from the group consisting of hydrogen and $(\text{C}_1-$
6 $\text{C}_8)$ alkyl;

7 Y is a divalent linkage selected from the group consisting of $-\text{N}(\text{R}^{12})-\text{S}(\text{O})_2-$,
8 wherein

9 R^{12} is a member selected from the group consisting of hydrogen and $(\text{C}_1-$
10 $\text{C}_8)$ alkyl;

11 R^1 is a member selected from the group consisting of hydrogen, halogen, $(\text{C}_1-$
12 $\text{C}_8)$ alkyl, (C_2-C_8) heteroalkyl, (C_1-C_8) alkoxy, $-\text{C}(\text{O})\text{R}^{14}$, $-\text{CO}_2\text{R}^{14}$,
13 $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{16}$, $-\text{S}(\text{O})_p-\text{R}^{14}$, $-\text{S}(\text{O})_q-\text{NR}^{15}\text{R}^{16}$, $-\text{O}-\text{C}(\text{O})-\text{R}^{17}$, and $-\text{N}(\text{R}^{14})-$
14 $\text{C}(\text{O})-\text{R}^{17}$;

15 wherein

16 R^{14} is a member selected from the group consisting of hydrogen, $(\text{C}_1-$
17 $\text{C}_8)$ alkyl, hetero (C_1-C_8) alkyl, aryl and aryl (C_1-C_4) alkyl;

18 R^{15} and R^{16} are members independently selected from the group consisting
19 of hydrogen, (C_1-C_8) alkyl and (C_2-C_8) heteroalkyl, or taken together
20 with the nitrogen to which each is attached form a 5-, 6- or 7-
21 membered ring;

22 R^{17} is a member selected from the group consisting of hydrogen, $(\text{C}_1-$
23 $\text{C}_8)$ alkyl and (C_2-C_8) heteroalkyl;

24 the subscript p is an integer of from 0 to 2; and

25 the subscript q is 2; and

26 R^2 is a substituted or unsubstituted phenyl; and

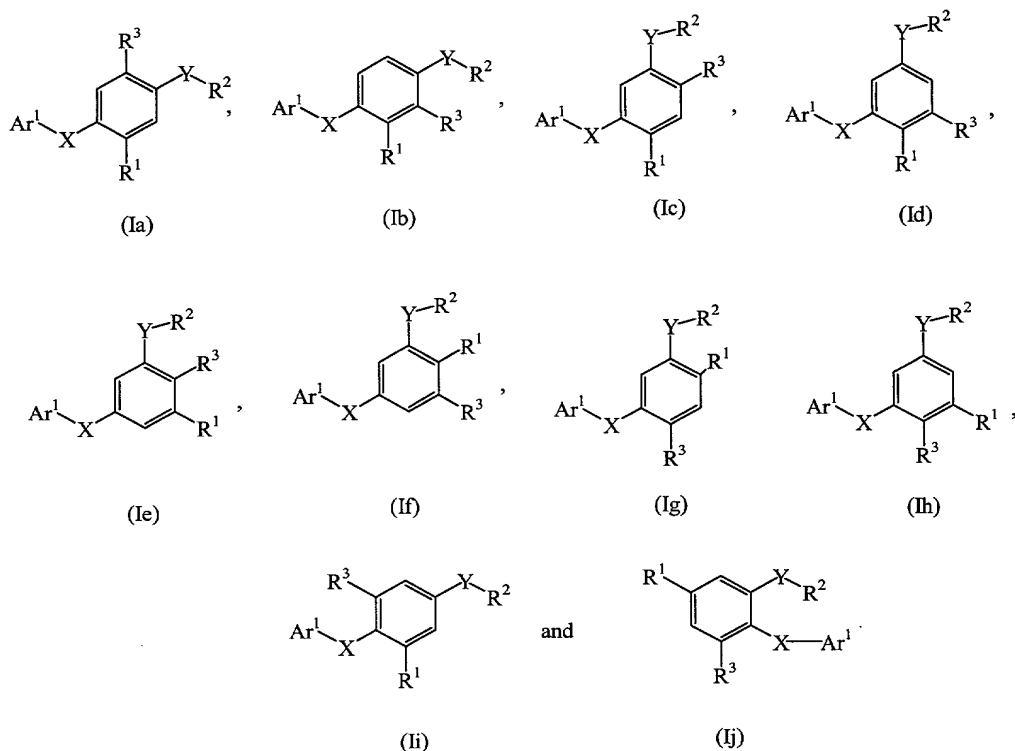
27 R^3 is a member selected from the group consisting of halogen and (C_1-C_8) alkoxy.

1 7. A compound of claim 6, wherein X is -O-, -NH- or -S-; Y is
2 -NH-SO₂-; R¹ is a member selected from the group consisting of halogen, (C₁-C₈)alkyl,
3 (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and
4 -S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from the
5 group consisting of halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -
6 CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from the group consisting of halogen,
7 methoxy and trifluoromethoxy.

1 8. A compound of claim 7, wherein Ar¹ is a phenyl group having
2 from 1 to 3 substituents selected from the group consisting of halogen, -OCF₃, -OH, -
3 O(C₁-C₆)alkyl, -CF₃, (C₁-C₈)alkyl and -NO₂; R¹ is a member selected from the group
4 consisting of halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and (C₁-C₈)alkoxy; R² is a phenyl
5 group having from 0 to 3 substituents selected from the group consisting of halogen, -
6 OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and
7 R³ is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

1 9. A compound of claim 2, wherein Ar¹ is a substituted or
2 unsubstituted pyridyl group.

1 10. A compound of claim 9, represented by a formula selected from the
2 group consisting of

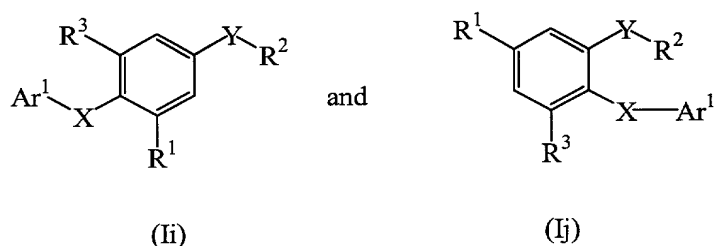


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11. A compound of claim 10, represented by a formula selected from the group consisting of



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12. A compound of claim 11, wherein

X is a divalent linkage selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{11})-$ and $-\text{S}-$;

wherein

R^{11} is a member selected from the group consisting of hydrogen and $(\text{C}_1-\text{C}_8)\text{alkyl}$;

Y is a divalent linkage selected from the group consisting of $-\text{N}(\text{R}^{12})-\text{S}(\text{O})_2-$,

wherein

R^{12} is a member selected from the group consisting of hydrogen and $(\text{C}_1-\text{C}_8)\text{alkyl}$;

R^1 is a member selected from the group consisting of hydrogen, halogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$, $(\text{C}_1-\text{C}_8)\text{alkoxy}$, $-\text{C}(\text{O})\text{R}^{14}$, $-\text{CO}_2\text{R}^{14}$,

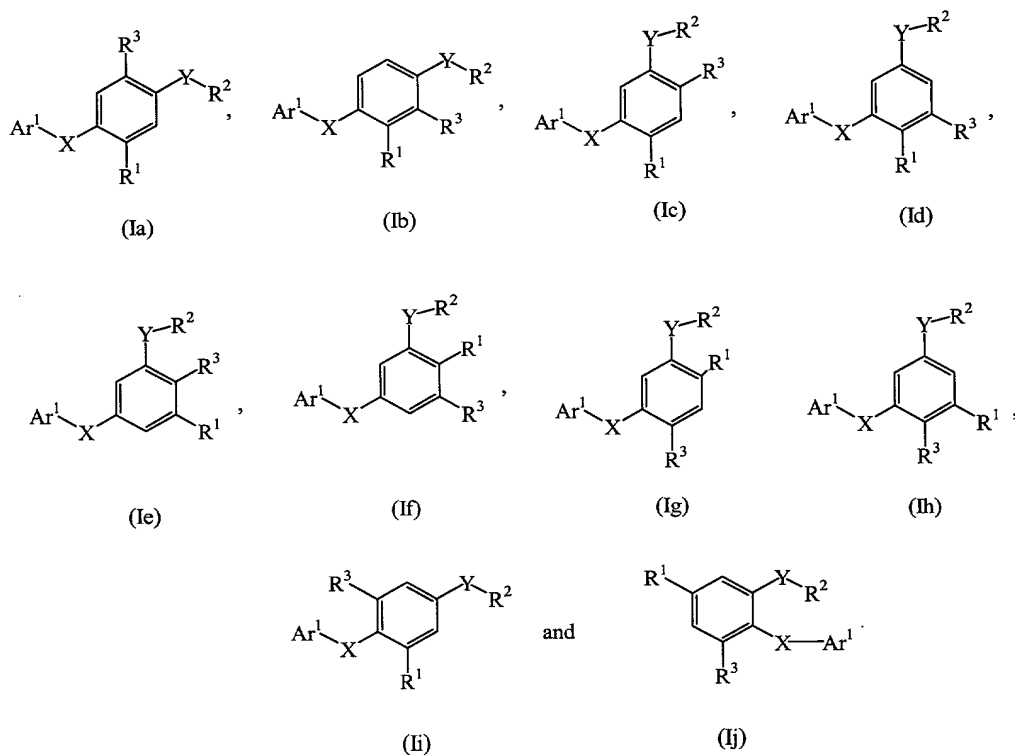
13 $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{16}$, $-\text{S}(\text{O})_p-\text{R}^{14}$, $-\text{S}(\text{O})_q-\text{NR}^{15}\text{R}^{16}$, $-\text{O}-\text{C}(\text{O})-\text{R}^{17}$, and $-\text{N}(\text{R}^{14})-$
 14 $\text{C}(\text{O})-\text{R}^{17}$;
 15 wherein
 16 R^{14} is a member selected from the group consisting of hydrogen, $(\text{C}_1-$
 17 $\text{C}_8)\text{alkyl}$, hetero $(\text{C}_1-\text{C}_8)\text{alkyl}$, aryl and aryl $(\text{C}_1-\text{C}_4)\text{alkyl}$;
 18 R^{15} and R^{16} are members independently selected from the group consisting
 19 of hydrogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$, or taken together
 20 with the nitrogen to which each is attached form a 5-, 6- or 7-
 21 membered ring;
 22 R^{17} is a member selected from the group consisting of hydrogen, $(\text{C}_1-$
 23 $\text{C}_8)\text{alkyl}$ and $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$;
 24 the subscript p is an integer of from 0 to 2; and
 25 the subscript q is 2; and
 26 R^2 is a substituted or unsubstituted phenyl; and
 27 R^3 is a member selected from the group consisting of halogen and $(\text{C}_1-\text{C}_8)\text{alkoxy}$.

1 13. A compound of claim 12, wherein X is $-\text{O}-$, $-\text{NH}-$ or $-\text{S}-$; Y is
 2 $-\text{NH}-\text{SO}_2-$; R^1 is a member selected from the group consisting of halogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$,
 3 $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$, $(\text{C}_1-\text{C}_8)\text{alkoxy}$, $-\text{C}(\text{O})\text{R}^{14}$, $-\text{CO}_2\text{R}^{14}$, $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{16}$, $-\text{S}(\text{O})_p-\text{R}^{14}$ and
 4 $-\text{S}(\text{O})_q-\text{NR}^{15}\text{R}^{16}$; R^2 is a phenyl group having from 0 to 3 substituents selected from the
 5 group consisting of halogen, $-\text{OCF}_3$, $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_8)\text{alkyl}$, $-\text{C}(\text{O})-(\text{C}_1-\text{C}_8)\text{alkyl}$, $-\text{CN}$, $-\text{CF}_3$, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $-\text{NH}_2$; and R^3 is selected from the group consisting of halogen,
 6 methoxy and trifluoromethoxy.

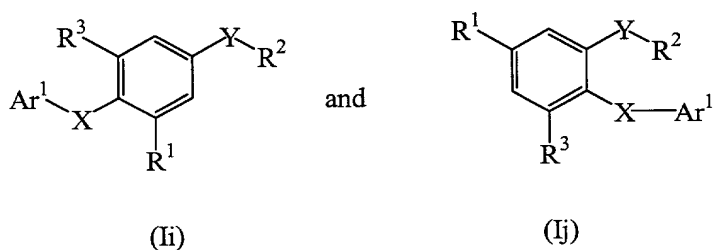
1 14. A compound of claim 13, wherein Ar^1 is a pyridyl group having
 2 from 1 to 3 substituents selected from the group consisting of halogen, $-\text{OCF}_3$, $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{CF}_3$, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $-\text{NO}_2$; R^1 is a member selected from the group
 3 consisting of halogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$ and $(\text{C}_1-\text{C}_8)\text{alkoxy}$; R^2 is a phenyl
 4 group having from 0 to 3 substituents selected from the group consisting of halogen, $-\text{OCF}_3$, $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_8)\text{alkyl}$, $-\text{C}(\text{O})-(\text{C}_1-\text{C}_8)\text{alkyl}$, $-\text{CN}$, $-\text{CF}_3$, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $-\text{NH}_2$; and
 5 R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

1 15. A compound of claim 2, wherein Ar^1 is a substituted or
 2 unsubstituted naphthyl group.

1 16. A compound of claim 15, represented by a formula selected from
 2 the group consisting of



17. A compound of claim 16, represented by a formula selected from the group consisting of



18. A compound of claim 17, wherein

X is a divalent linkage selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{11})-$ and $-\text{S}-$;

wherein

R^{11} is a member selected from the group consisting of hydrogen and $(\text{C}_1-\text{C}_8)\text{alkyl}$;

Y is a divalent linkage selected from the group consisting of $-\text{N}(\text{R}^{12})-\text{S}(\text{O})_2-$,

wherein

R^{12} is a member selected from the group consisting of hydrogen and $(\text{C}_1-\text{C}_8)\text{alkyl}$;

R^1 is a member selected from the group consisting of hydrogen, halogen, $(\text{C}_1-$

C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴,
-C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴, -S(O)_q-NR¹⁵R¹⁶, -O-C(O)-R¹⁷, and -N(R¹⁴)-
C(O)-R¹⁷;

wherein

R¹⁴ is a member selected from the group consisting of hydrogen, (C₁-
C₈)alkyl, hetero(C₁-C₈)alkyl, aryl and aryl(C₁-C₄)alkyl;

R¹⁵ and R¹⁶ are members independently selected from the group consisting
of hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl, or taken together
with the nitrogen to which each is attached form a 5-, 6- or 7-
membered ring;

R¹⁷ is a member selected from the group consisting of hydrogen, (C₁-
C₈)alkyl and (C₂-C₈)heteroalkyl;

the subscript p is an integer of from 0 to 2; and

the subscript q is 2; and

R² is a substituted or unsubstituted phenyl; and

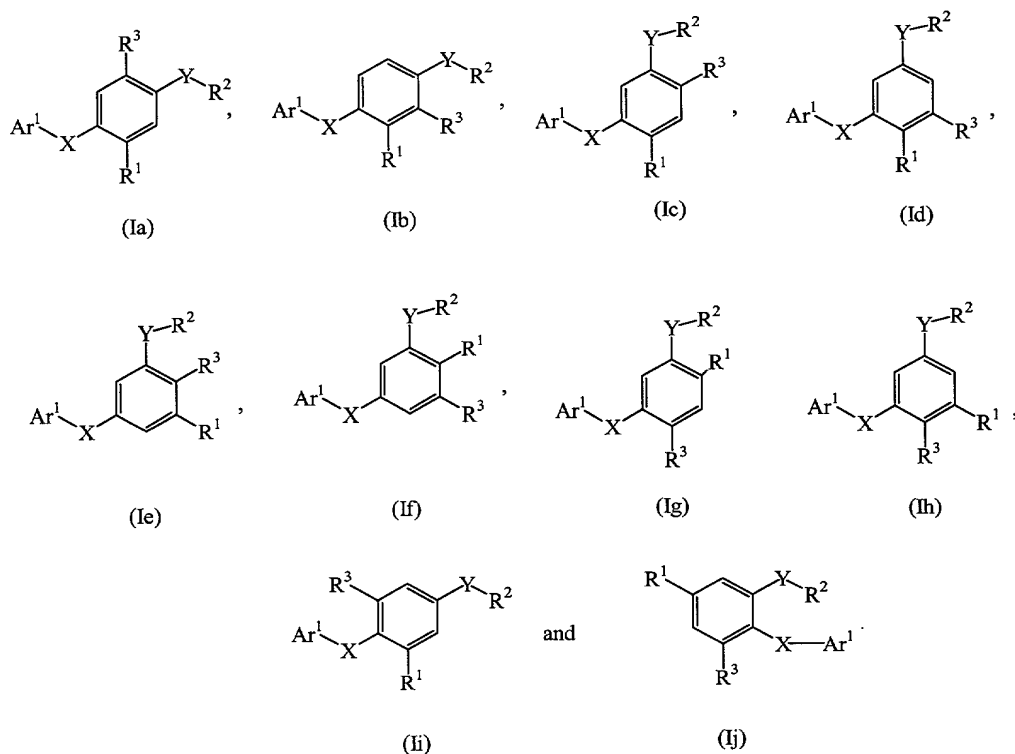
R³ is a member selected from the group consisting of halogen and (C₁-C₈)alkoxy.

19. A compound of claim 18, wherein X is -O-, -NH- or -S-; Y is
-NH-SO₂-; R¹ is a member selected from the group consisting of halogen, (C₁-C₈)alkyl,
(C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and
-S(O)_q-NR¹⁵R¹⁶; R² is a phenyl group having from 0 to 3 substituents selected from the
group consisting of halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -
CF₃, (C₁-C₈)alkyl and -NH₂; and R³ is selected from the group consisting of halogen,
methoxy and trifluoromethoxy.

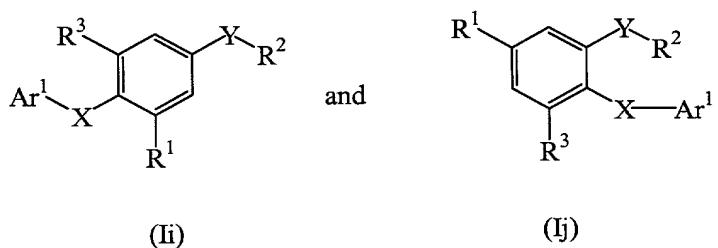
20. A compound of claim 19, wherein Ar¹ is a naphthyl group having
from 1 to 3 substituents selected from the group consisting of halogen, -OCF₃, -OH, -
O(C₁-C₆)alkyl, -CF₃, (C₁-C₈)alkyl and -NO₂; R¹ is a member selected from the group
consisting of halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and (C₁-C₈)alkoxy; R² is a phenyl
group having from 0 to 3 substituents selected from the group consisting of halogen, -
OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and
R³ is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

21. A compound of claim 2, wherein Ar¹ is a substituted or
unsubstituted isoquinolinyl group.

1 **22.** A compound of claim 21, represented by a formula selected from
2 the group consisting of



1 **23.** A compound of claim 22, represented by a formula selected from
2 the group consisting of



1 **24.** A compound of claim 23, wherein
2 X is a divalent linkage selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$,
3 $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{11})-$ and $-\text{S}-$;
4 wherein
5 R^{11} is a member selected from the group consisting of hydrogen and $(\text{C}_1-$
6 $\text{C}_8)\text{alkyl}$;
7 Y is a divalent linkage selected from the group consisting of $-\text{N}(\text{R}^{12})-\text{S}(\text{O})_2-$,

wherein

R^{12} is a member selected from the group consisting of hydrogen and (C₁-C₈)alkyl;

R^1 is a member selected from the group consisting of hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O) R^{14} , -CO₂ R^{14} , -C(O)NR¹⁵ R^{16} , -S(O)_p- R^{14} , -S(O)_q-NR¹⁵ R^{16} , -O-C(O)- R^{17} , and -N(R^{14})-C(O)- R^{17} ;

wherein

R^{14} is a member selected from the group consisting of hydrogen, (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, aryl and aryl(C₁-C₄)alkyl;

R^{15} and R^{16} are members independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;

R^{17} is a member selected from the group consisting of hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl;

the subscript p is an integer of from 0 to 2; and

the subscript q is 2; and

R^2 is a substituted or unsubstituted phenyl; and

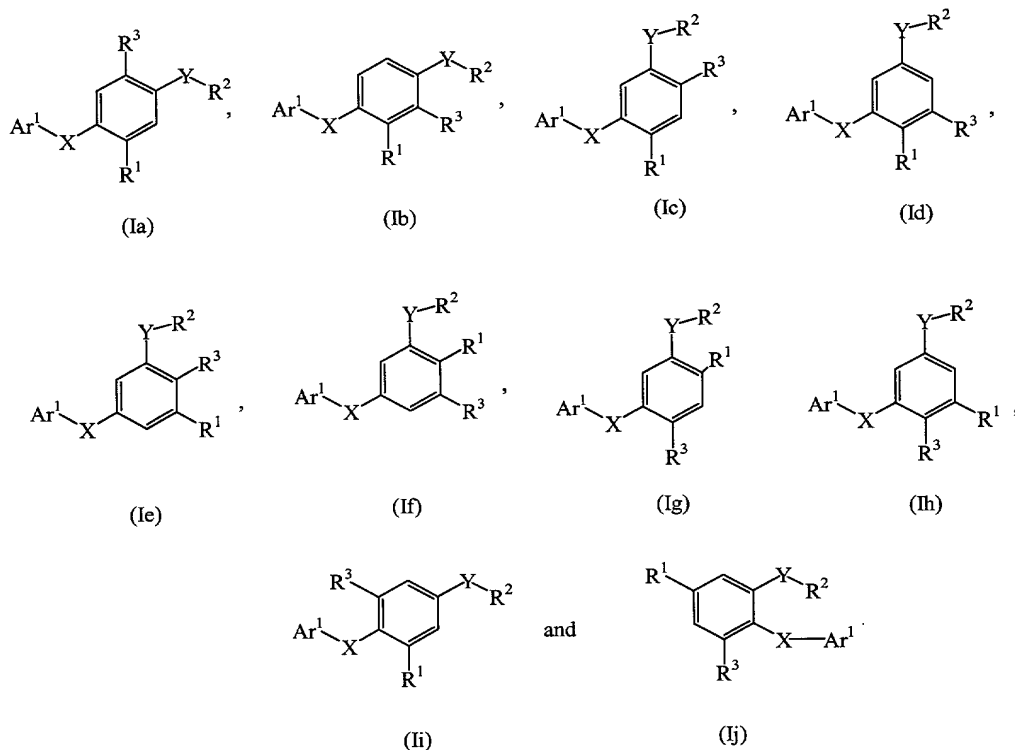
R^3 is a member selected from the group consisting of halogen and (C₁-C₈)alkoxy.

25. A compound of claim 24, wherein X is -O-, -NH- or -S-; Y is -NH-SO₂-; R^1 is a member selected from the group consisting of halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O) R^{14} , -CO₂ R^{14} , -C(O)NR¹⁵ R^{16} , -S(O)_p- R^{14} and -S(O)_q-NR¹⁵ R^{16} ; R^2 is a phenyl group having from 0 to 3 substituents selected from the group consisting of halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

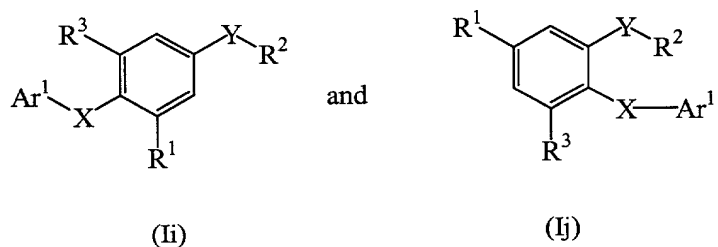
26. A compound of claim 25, wherein Ar¹ is a isoquinolinyl group having from 1 to 3 substituents selected from the group consisting of halogen, -OCF₃, -OH, -O(C₁-C₆)alkyl, -CF₃, (C₁-C₈)alkyl and -NO₂; R^1 is a member selected from the group consisting of halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and (C₁-C₈)alkoxy; R^2 is a phenyl group having from 0 to 3 substituents selected from the group consisting of halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

1 27. A compound of claim 2, wherein Ar¹ is a substituted or
2 unsubstituted benzoxazolyl group.

1 28. A compound of claim 27, represented by a formula selected from
2 the group consisting of



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1 29. A compound of claim 28, represented by a formula selected from
2 the group consisting of



1 30. A compound of claim 29, wherein
2 X is a divalent linkage selected from the group consisting of -CH₂-, -CH(CH₃)-,
3 -O-, -C(O)-, -N(R¹¹)- and -S-;
4 wherein

R^{11} is a member selected from the group consisting of hydrogen and (C₁-C₈)alkyl;
Y is a divalent linkage selected from the group consisting of -N(R¹²)-S(O)₂-,
wherein
 R^{12} is a member selected from the group consisting of hydrogen and (C₁-C₈)alkyl;
 R^1 is a member selected from the group consisting of hydrogen, halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴,
-C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴, -S(O)_q-NR¹⁵R¹⁶, -O-C(O)-R¹⁷, and -N(R¹⁴)-C(O)-R¹⁷;
wherein
 R^{14} is a member selected from the group consisting of hydrogen, (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, aryl and aryl(C₁-C₄)alkyl;
 R^{15} and R^{16} are members independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;
 R^{17} is a member selected from the group consisting of hydrogen, (C₁-C₈)alkyl and (C₂-C₈)heteroalkyl;
the subscript p is an integer of from 0 to 2; and
the subscript q is 2; and
 R^2 is a substituted or unsubstituted phenyl; and
 R^3 is a member selected from the group consisting of halogen and (C₁-C₈)alkoxy.

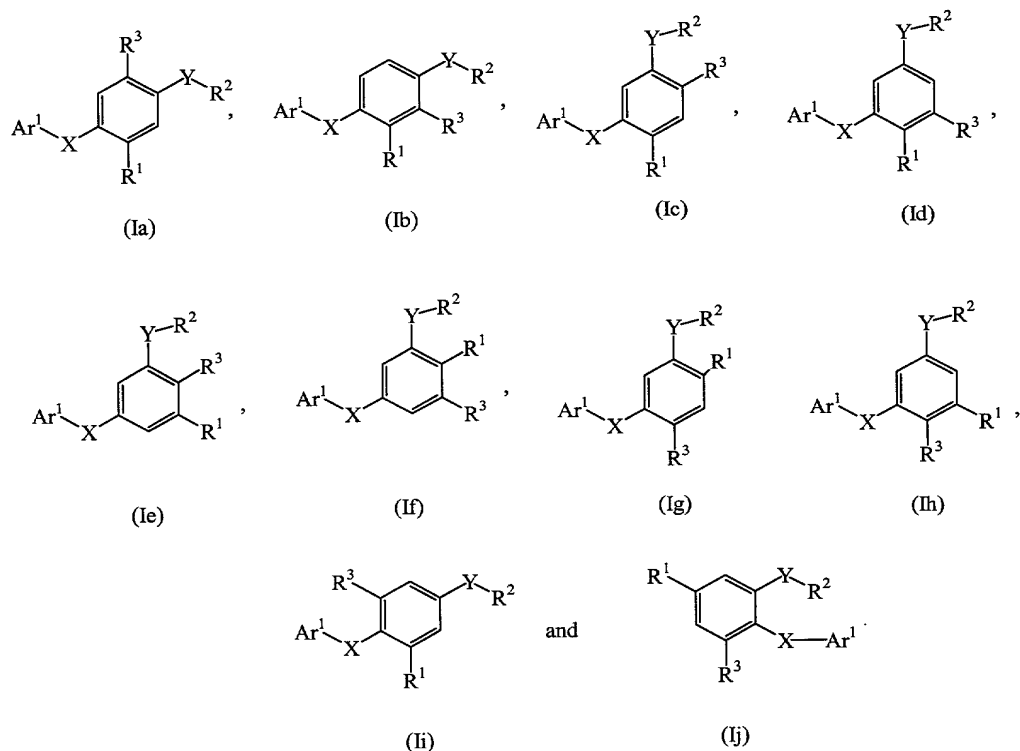
31. A compound of claim 30, wherein X is -O-, -NH- or -S-; Y is -NH-SO₂-; R^1 is a member selected from the group consisting of halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, (C₁-C₈)alkoxy, -C(O)R¹⁴, -CO₂R¹⁴, -C(O)NR¹⁵R¹⁶, -S(O)_p-R¹⁴ and -S(O)_q-NR¹⁵R¹⁶; R^2 is a phenyl group having from 0 to 3 substituents selected from the group consisting of halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -NH₂; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

32. A compound of claim 31, wherein Ar¹ is a benzoxazolyl group having from 1 to 3 substituents selected from the group consisting of halogen, -OCF₃, -OH, -O(C₁-C₆)alkyl, -CF₃, (C₁-C₈)alkyl and -NO₂; R^1 is a member selected from the group consisting of halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and (C₁-C₈)alkoxy; R^2 is a phenyl group having from 0 to 3 substituents selected from the group consisting of

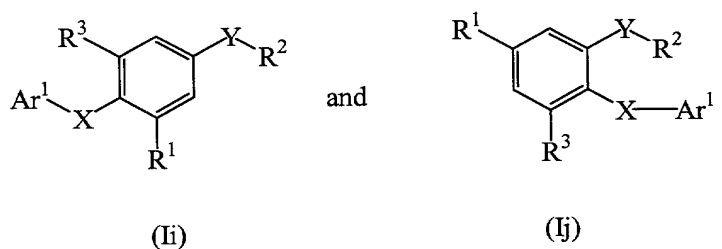
6 halogen, $-\text{OCF}_3$, $-\text{OH}$, $-\text{O}(\text{C}_1\text{-C}_8)\text{alkyl}$, $-\text{C}(\text{O})-(\text{C}_1\text{-C}_8)\text{alkyl}$, $-\text{CN}$, $-\text{CF}_3$, $(\text{C}_1\text{-C}_8)\text{alkyl}$ and -
 7 NH_2 ; and R^3 is selected from the group consisting of halogen, methoxy and
 8 trifluoromethoxy.

1 33. A compound of claim 2, wherein Ar^1 is a substituted or
 2 unsubstituted benzimidazolyl group.

1 34. A compound of claim 33, represented by a formula selected from
 2 the group consisting of



1 35. A compound of claim 34, represented by a formula selected from
 2 the group consisting of



1 36. A compound of claim 35, wherein

2 X is a divalent linkage selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$,
3 $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{11})-$ and $-\text{S}-$;

4 wherein

5 R^{11} is a member selected from the group consisting of hydrogen and $(\text{C}_1-$
6 $\text{C}_8)\text{alkyl}$;

7 Y is a divalent linkage selected from the group consisting of $-\text{N}(\text{R}^{12})-\text{S}(\text{O})_2-$,
8 wherein

9 R^{12} is a member selected from the group consisting of hydrogen and $(\text{C}_1-$
10 $\text{C}_8)\text{alkyl}$;

11 R^1 is a member selected from the group consisting of hydrogen, halogen, $(\text{C}_1-$
12 $\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$, $(\text{C}_1-\text{C}_8)\text{alkoxy}$, $-\text{C}(\text{O})\text{R}^{14}$, $-\text{CO}_2\text{R}^{14}$,
13 $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{16}$, $-\text{S}(\text{O})_p-\text{R}^{14}$, $-\text{S}(\text{O})_q-\text{NR}^{15}\text{R}^{16}$, $-\text{O}-\text{C}(\text{O})-\text{R}^{17}$, and $-\text{N}(\text{R}^{14})-$
14 $\text{C}(\text{O})-\text{R}^{17}$;

15 wherein

16 R^{14} is a member selected from the group consisting of hydrogen, $(\text{C}_1-$
17 $\text{C}_8)\text{alkyl}$, hetero $(\text{C}_1-\text{C}_8)\text{alkyl}$, aryl and aryl $(\text{C}_1-\text{C}_4)\text{alkyl}$;

18 R^{15} and R^{16} are members independently selected from the group consisting
19 of hydrogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$, or taken together
20 with the nitrogen to which each is attached form a 5-, 6- or 7-
21 membered ring;

22 R^{17} is a member selected from the group consisting of hydrogen, $(\text{C}_1-$
23 $\text{C}_8)\text{alkyl}$ and $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$;

24 the subscript p is an integer of from 0 to 2; and

25 the subscript q is 2; and

26 R^2 is a substituted or unsubstituted phenyl; and

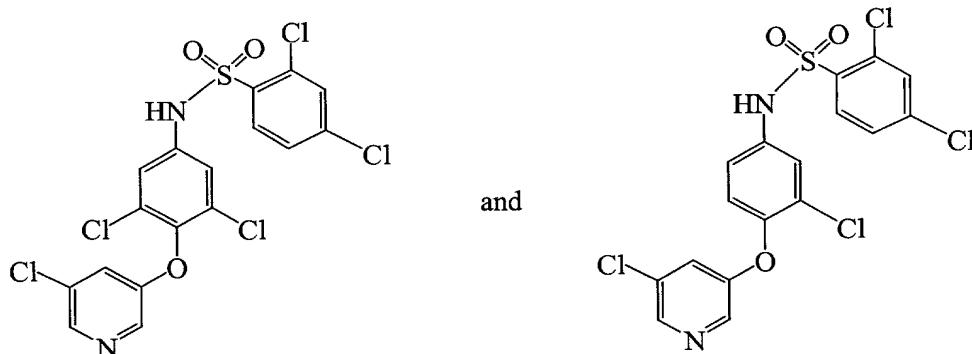
27 R^3 is a member selected from the group consisting of halogen and $(\text{C}_1-\text{C}_8)\text{alkoxy}$.

1 37. A compound of claim 36, wherein X is $-\text{O}-$, $-\text{NH}-$ or $-\text{S}-$; Y is
2 $-\text{NH}-\text{SO}_2-$; R^1 is a member selected from the group consisting of halogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$,
3 $(\text{C}_2-\text{C}_8)\text{heteroalkyl}$, $(\text{C}_1-\text{C}_8)\text{alkoxy}$, $-\text{C}(\text{O})\text{R}^{14}$, $-\text{CO}_2\text{R}^{14}$, $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{16}$, $-\text{S}(\text{O})_p-\text{R}^{14}$ and
4 $-\text{S}(\text{O})_q-\text{NR}^{15}\text{R}^{16}$; R^2 is a phenyl group having from 0 to 3 substituents selected from the
5 group consisting of halogen, $-\text{OCF}_3$, $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_8)\text{alkyl}$, $-\text{C}(\text{O})-(\text{C}_1-\text{C}_8)\text{alkyl}$, $-\text{CN}$, $-\text{CF}_3$,
6 $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $-\text{NH}_2$; and R^3 is selected from the group consisting of halogen,
7 methoxy and trifluoromethoxy.

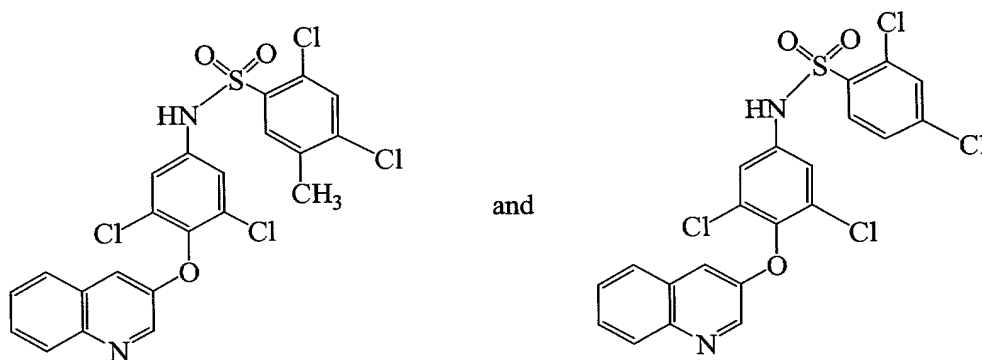
1 38. A compound of claim 37, wherein Ar^1 is a benzimidazolyl group
2 having from 1 to 3 substituents selected from the group consisting of halogen, $-\text{OCF}_3$, $-\text{OH}$,
3 $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{CF}_3$, $(\text{C}_1-\text{C}_8)\text{alkyl}$ and $-\text{NO}_2$; R^1 is a member selected from the

4 group consisting of halogen, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl and (C₁-C₈)alkoxy; R² is a
 5 phenyl group having from 0 to 3 substituents selected from the group consisting of
 6 halogen, -OCF₃, -OH, -O(C₁-C₈)alkyl, -C(O)-(C₁-C₈)alkyl, -CN, -CF₃, (C₁-C₈)alkyl and -
 7 NH₂; and R³ is selected from the group consisting of halogen, methoxy and
 8 trifluoromethoxy.

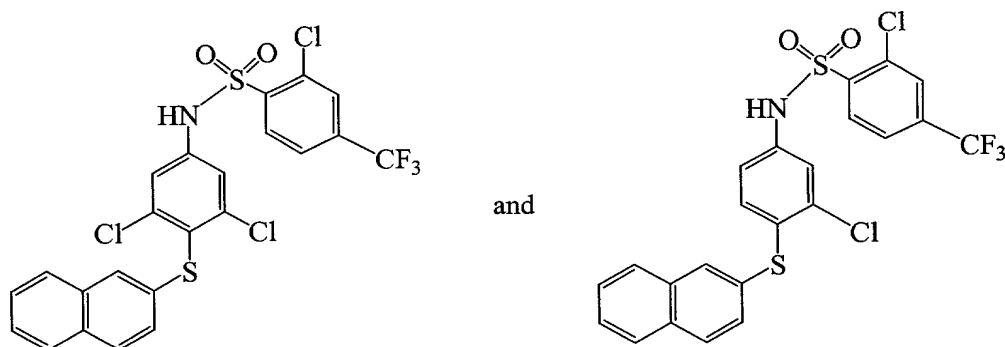
1 39. A compound of claim 1, selected from the group consisting of



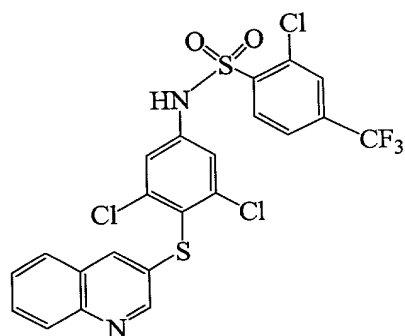
1 40. A compound of claim 1, selected from the group consisting of



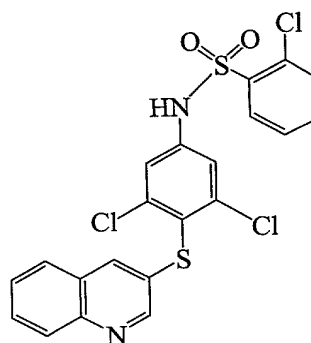
1 41. A compound of claim 1, selected from the group consisting of



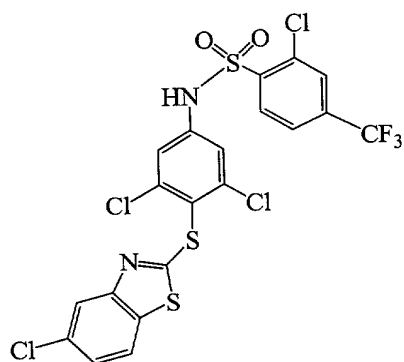
1 42. A compound of claim 1, selected from the group consisting of:



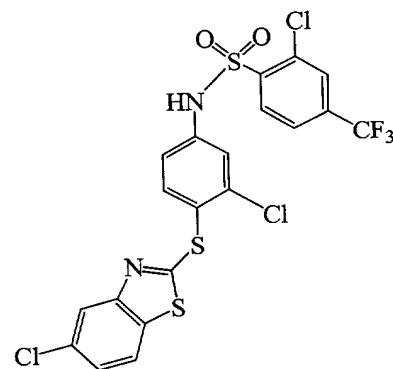
and



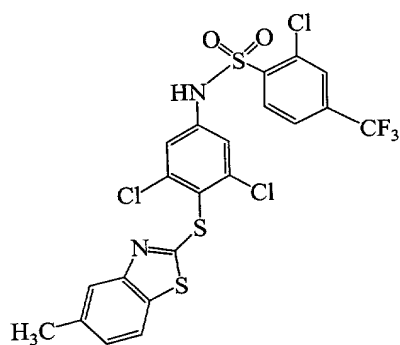
43. A compound of claim 1, selected from the group consisting of:



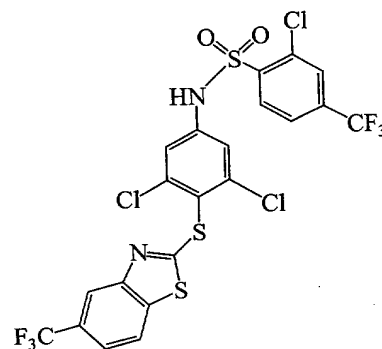
and



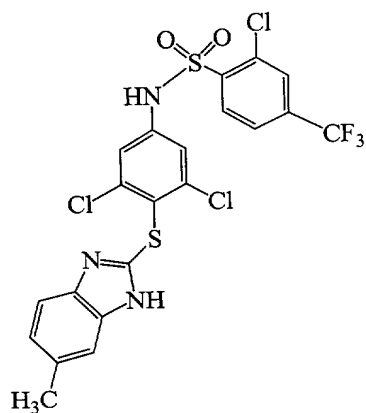
44. A compound of claim 1, selected from the group consisting of:



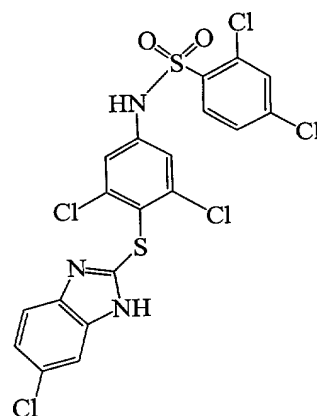
and



45. A compound of claim 1, selected from the group consisting of:



and



2

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46. A composition comprising a pharmaceutically acceptable excipient and a compound of any of claims 1-45.

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3

47. A method for modulating conditions associated with metabolic or inflammatory disorders in a host, said method comprising administering to said host an efficacious amount of a compound of any of claims 1-45.

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2

3

48. A method in accordance with claim 47, wherein said host is a mammal selected from the group consisting of humans, dogs, monkeys, mice, rats, horses and cats.

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2

49. A method in accordance with claim 47, wherein said administering is oral.

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2

50. A method in accordance with claim 47, wherein said administering is topical.

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2

51. A method in accordance with claim 47, wherein said administering is prophylactic to prevent the onset of a PPAR γ -mediated condition.

1

2

3

52. A method in accordance with claim 47, wherein said disorders are selected from the group consisting of NIDDM, obesity, hypercholesterolemia and other lipid-mediated diseases, and inflammatory conditions.

1

2

53. A method in accordance with claim 47, wherein said administering is parenteral.

COMPOUNDS FOR THE MODULATION OF PPAR γ ACTIVITY

ABSTRACT OF THE DISCLOSURE

- Modulators of PPAR γ activity are provided which are useful in
- 5 pharmaceutical compositions and methods for the treatment of conditions such as type II diabetes and obesity.

SF 1109766 v1

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **COMPOUNDS FOR THE MODULATION OF PPAR γ ACTIVITY** the specification of which is attached hereto, filed on June 28, 2000 as Application No. _____ and was amended on _____ (if applicable).

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56. I claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Country	Application No.	Date of Filing	Priority Claimed Under 35 USC 119

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date
60/141,672	June 30, 1999

I claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application No.	Date of Filing	Status

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

William B. Kezer, Reg. No. 37,369
Eugenia Garrett-Wackowski, Reg. No. 37,330

Send Correspondence to: William B. Kezer TOWNSEND and TOWNSEND and CREW LLP Two Embarcadero Center, 8th Floor San Francisco, California 94111-3834	Direct Telephone Calls to: (Name, Reg. No., Telephone No.) Name: William B. Kezer Reg. No.: 37,369 Telephone: 415-576-0200
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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 1 _____ Lawrence R. McGee	Signature of Inventor 2 _____ Jonathan B. Houze	Signature of Inventor 3 _____ Steven M. Rubenstein
Date	Date	Date